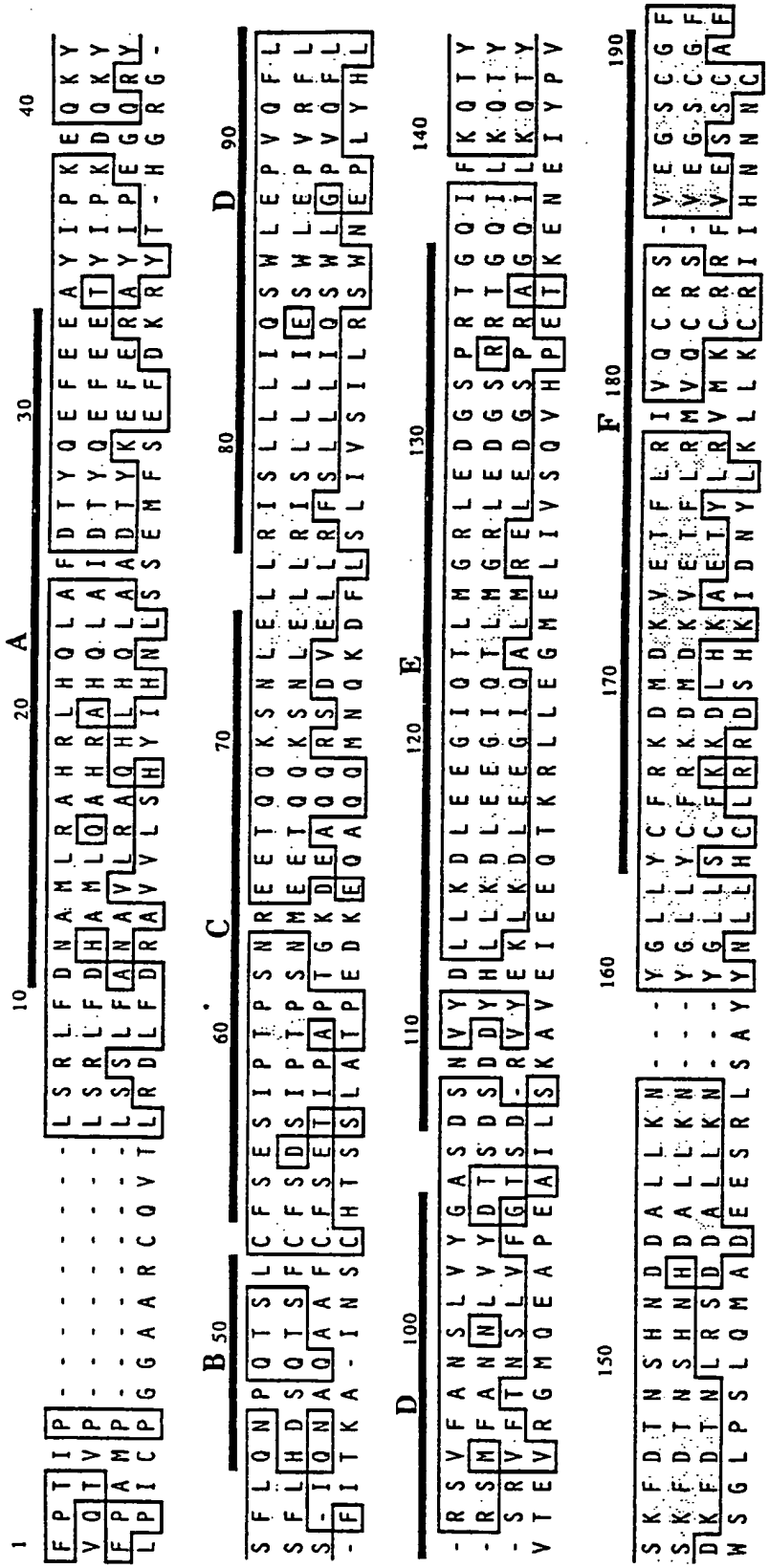


FIG.—2

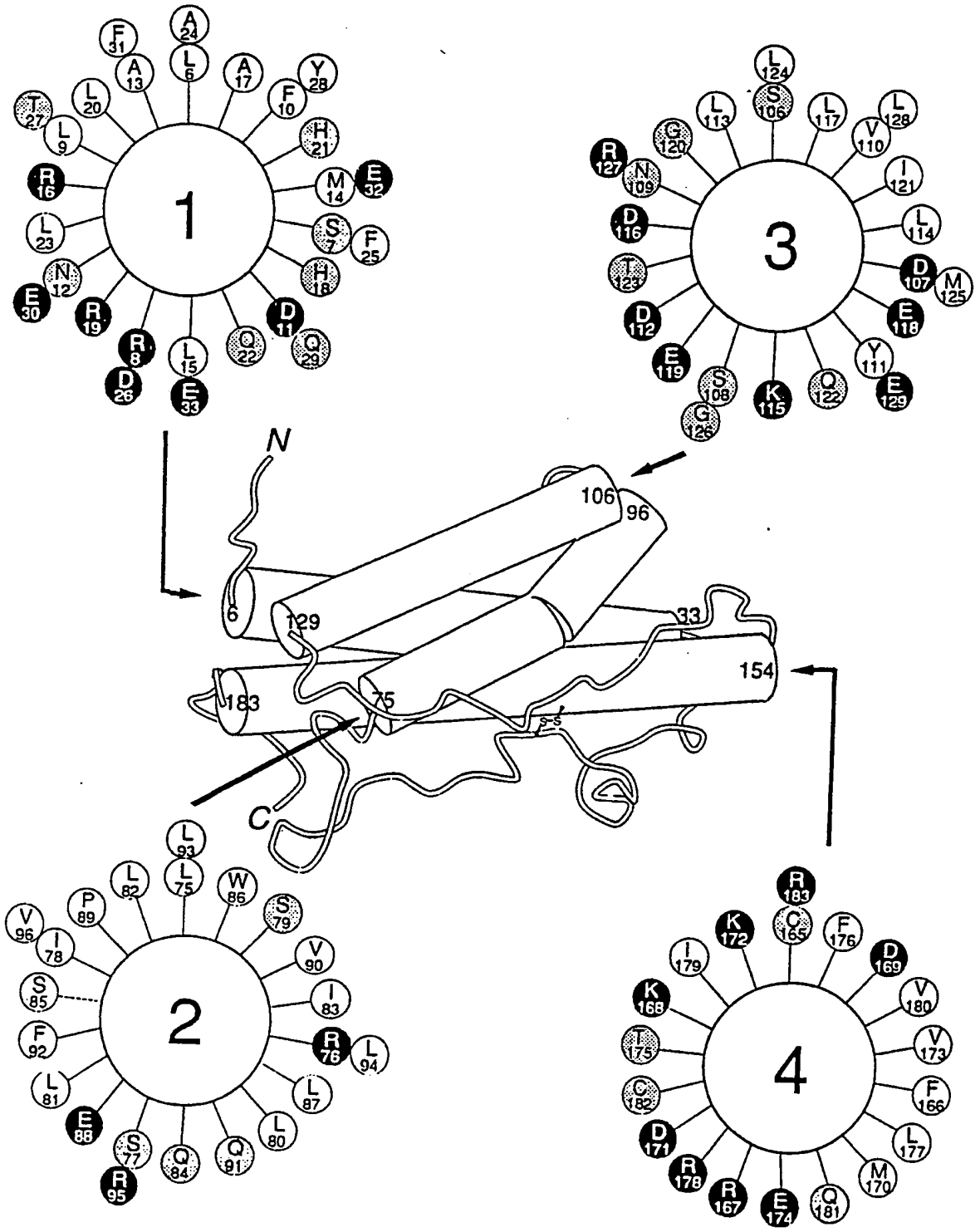


FIG.—3

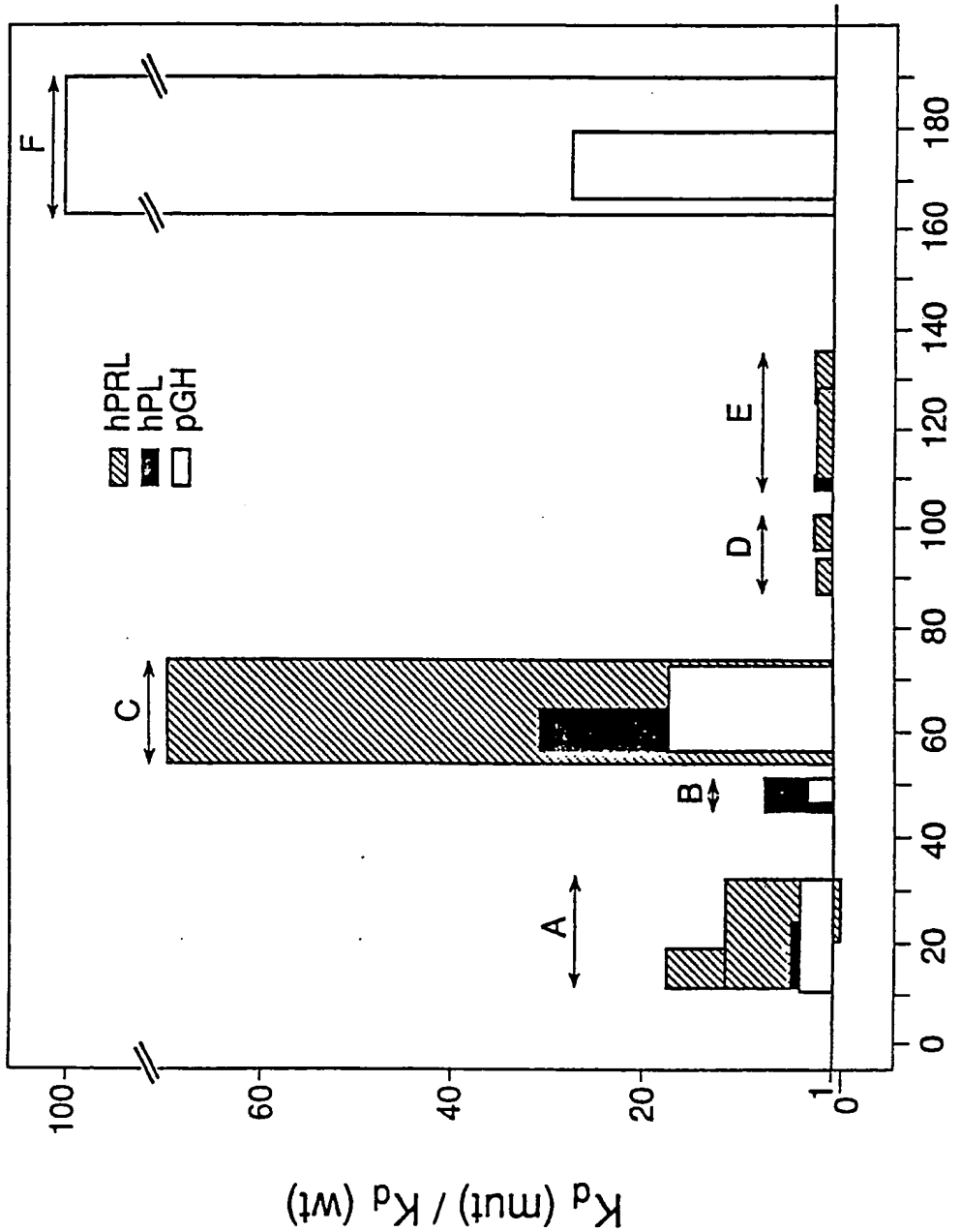

K_d (mut) / K_d (wt)
100
60
40
20
1
0
0
20
40
60
80
100
120
140
160
180
Residue number in hGH
hPRL
hPL
pGH
A
B
C
D
E
F

FIG.—4

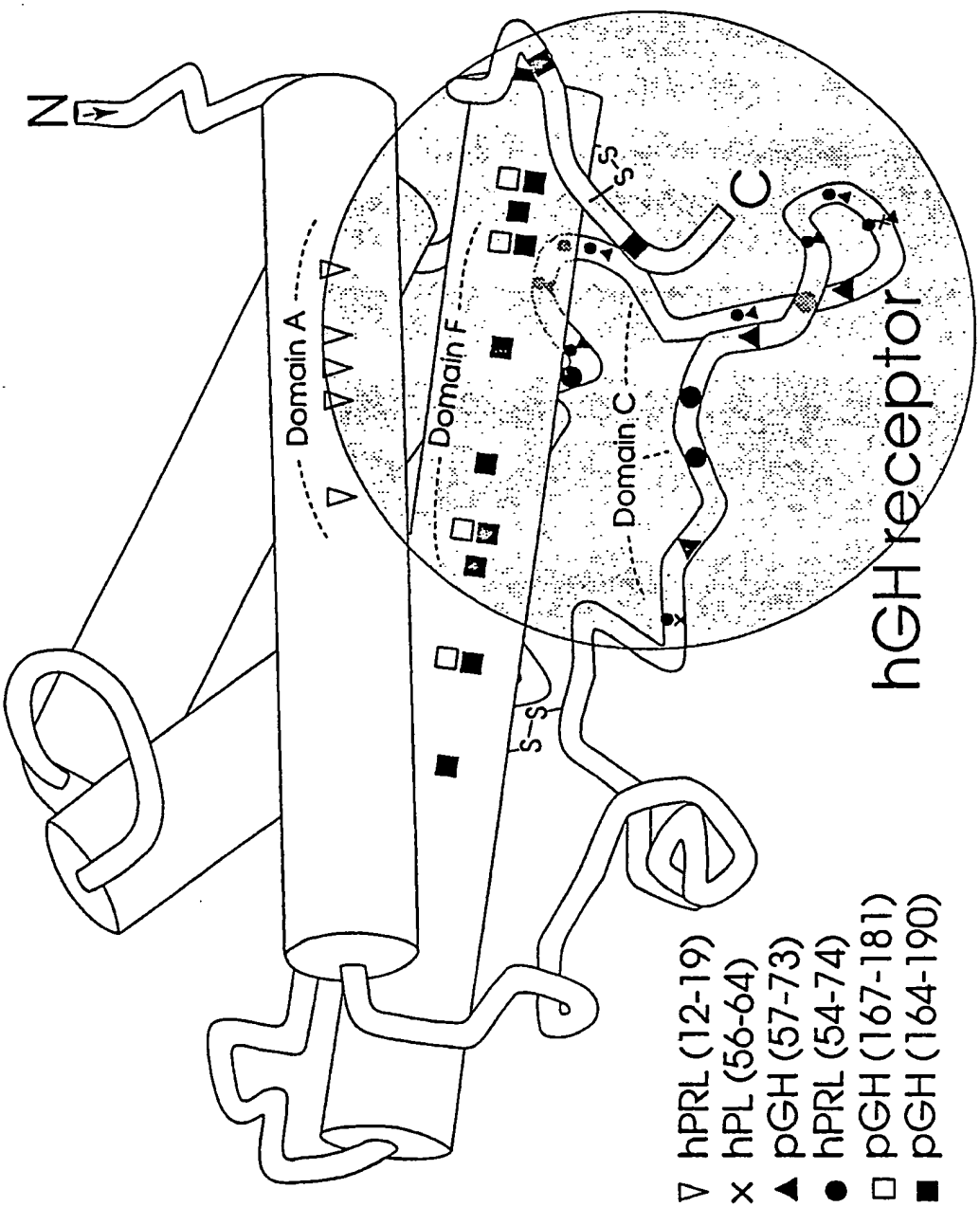

Z
Domain A
Domain F
Domain C
S-S
S-S
C
hGH receptor
▽ hPRL (12-19)
× hPL (56-64)
◀ ● pGH (57-73)
hPRL (54-74)
□ pGH (167-181)
■ pGH (164-190)

FIG.—5

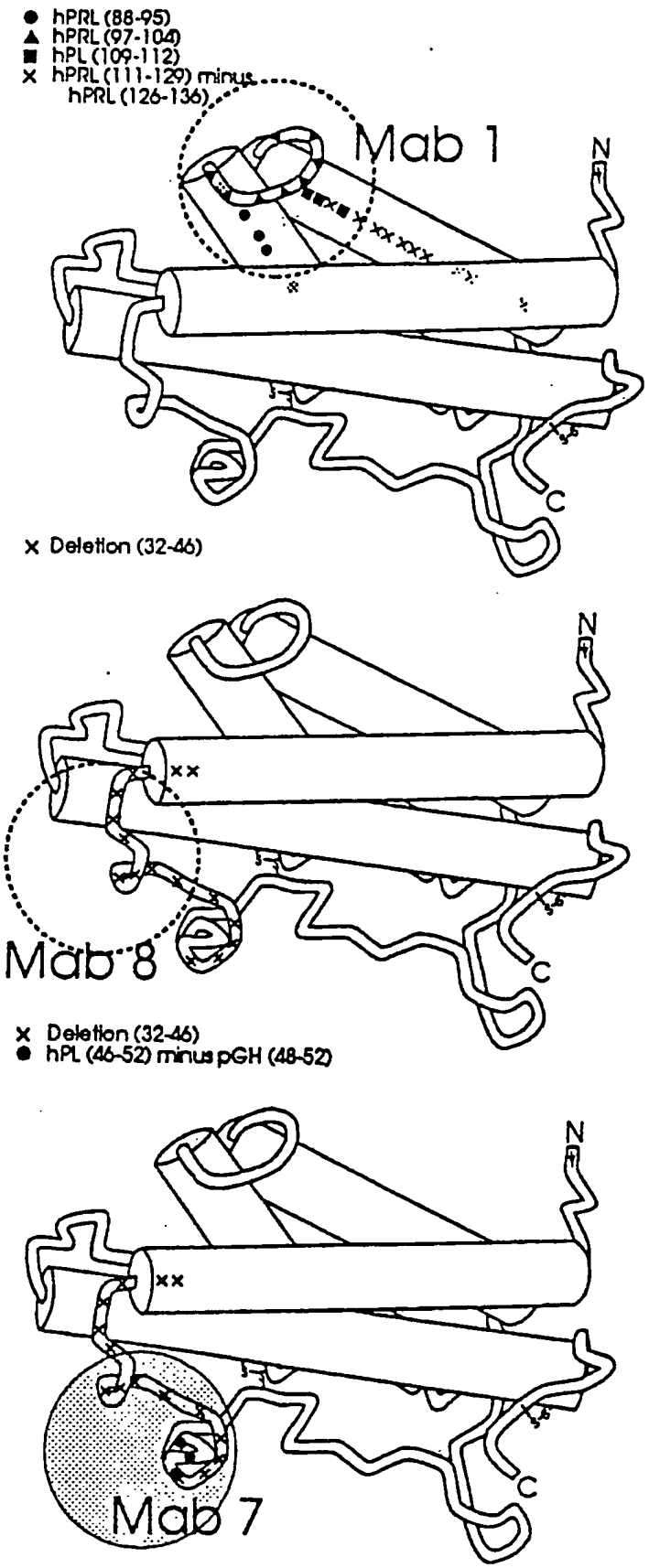
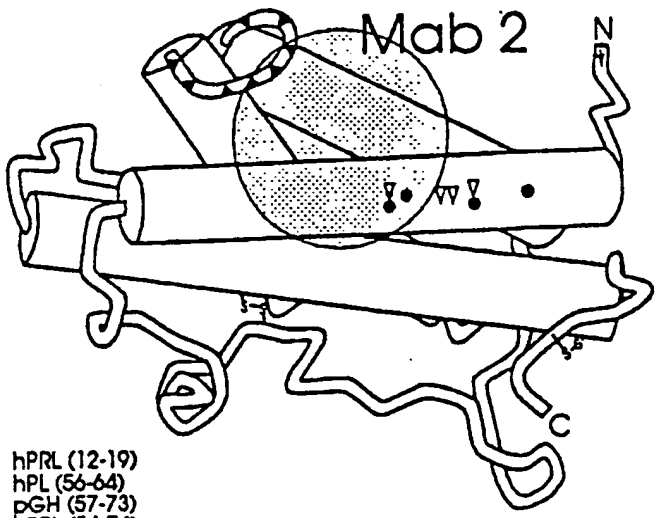


FIG.—6A

SUBSTITUTE SHEET

● pGH (11-33) minus hPRL (22-33)
▽ hPRL (12-19) minus hPL (12-25)
▲ hPRL (97-104)



▽ hPRL (12-19)
× hPL (56-64)
▲ pGH (57-73)
● hPRL (54-74)
□ pGH (167-181)
■ pGH (164-190)

▲ pGH (57-73) minus hPRL (54-74)
■ pGH (164-190) minus pGH (167-181)

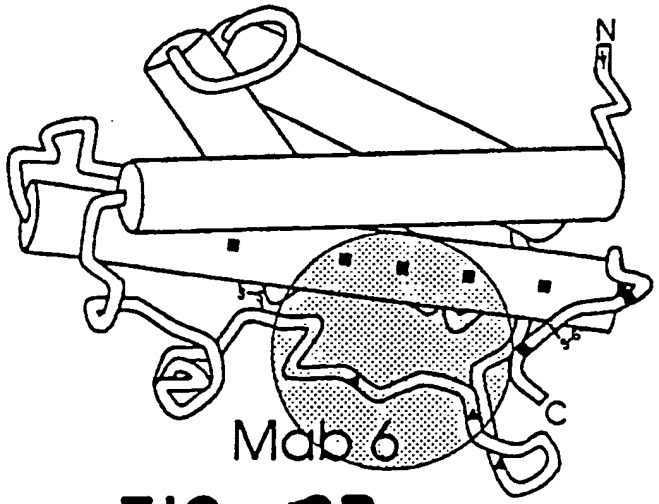
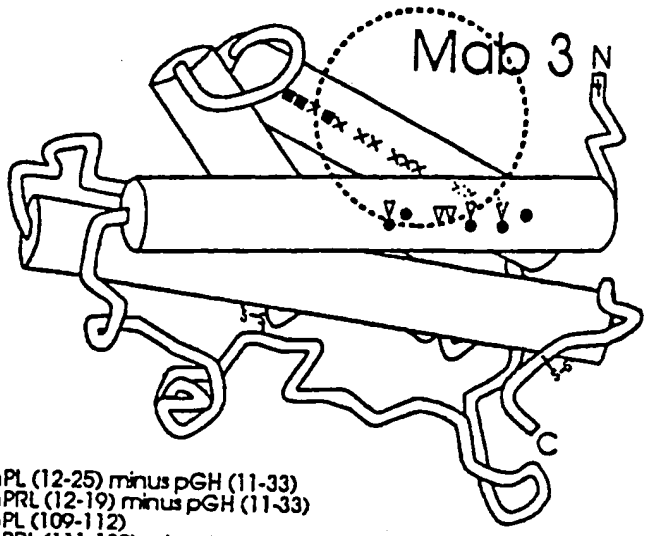


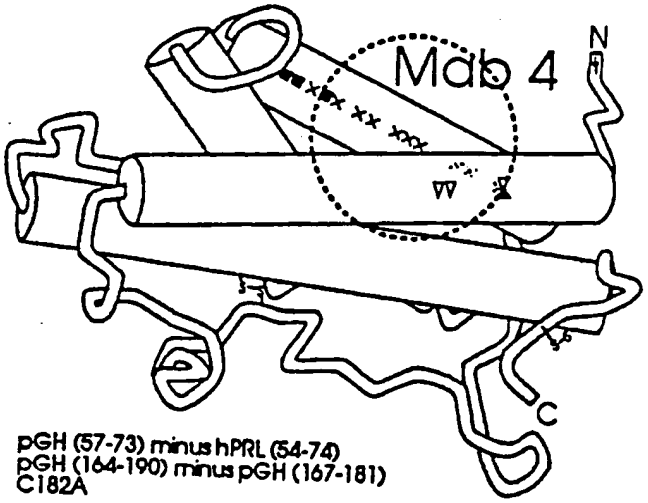
FIG.—6B

SUBSTITUTE SHEET

● pGH (11-33) minus hPRL (22-33)
▲ hPL (12-25) minus hPRL (22-33)
▽ hPRL (12-79)
■ hPL (109-112)
× hPRL (111-129) minus hPRL (126-136)



▲ hPL (12-25) minus pGH (11-33)
▽ hPRL (12-19) minus pGH (11-33)
■ hPL (109-112)
× hPRL (111-129) minus hPRL (126-136)



▲ pGH (57-73) minus hPRL (54-74)
■ pGH (164-190) minus pGH (167-181)
● C182A

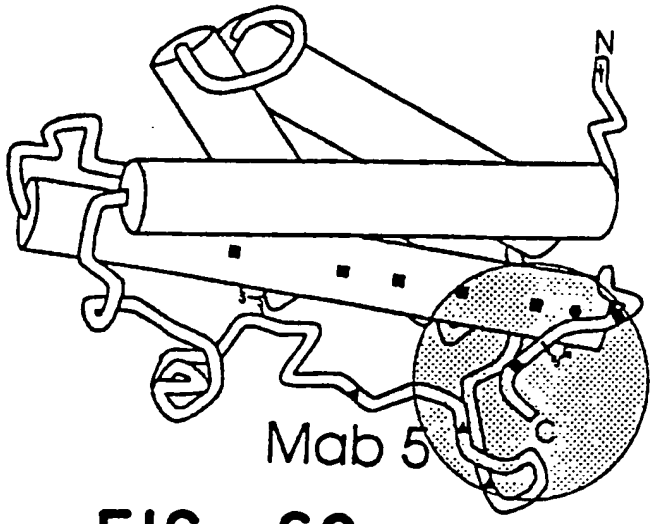


FIG.—6C

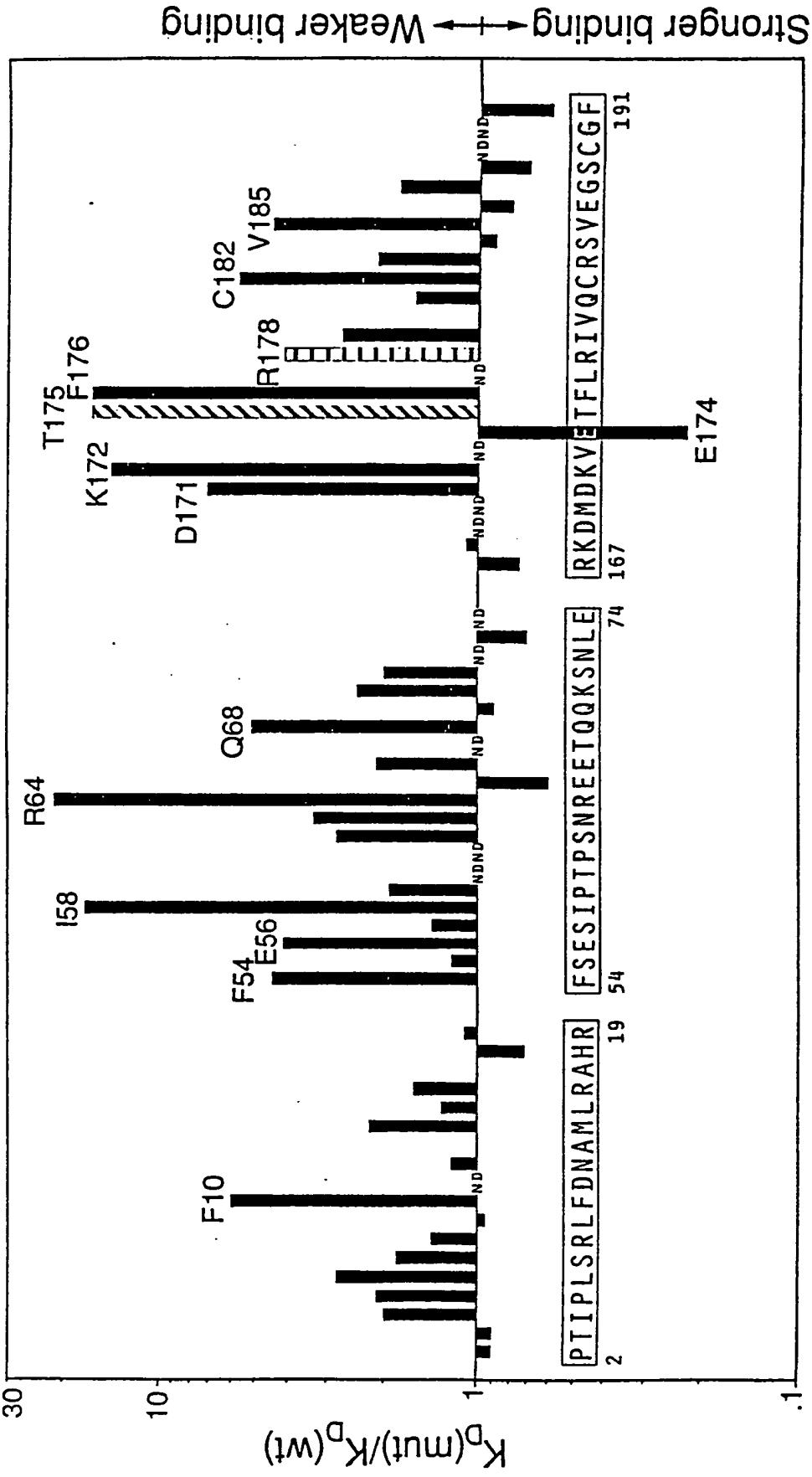

Stronger binding ← → Weaker binding
K_D(mut)/K_D(wt)
30
10
1
.1
PTIPLSRLFDNAMLRAHR
2
19
FSESIPTPSNREETQQKSNLE
54
74
RKDMDKVETFLRIVQCRSVEGSCGF
167
191
F10
I58
E56
F54
R64
Q68
K172
D171
T175
F176
R178
C182
V185
E174
ND
NDND

FIG.—7

hGH Synthetic Gene

FIG.—8

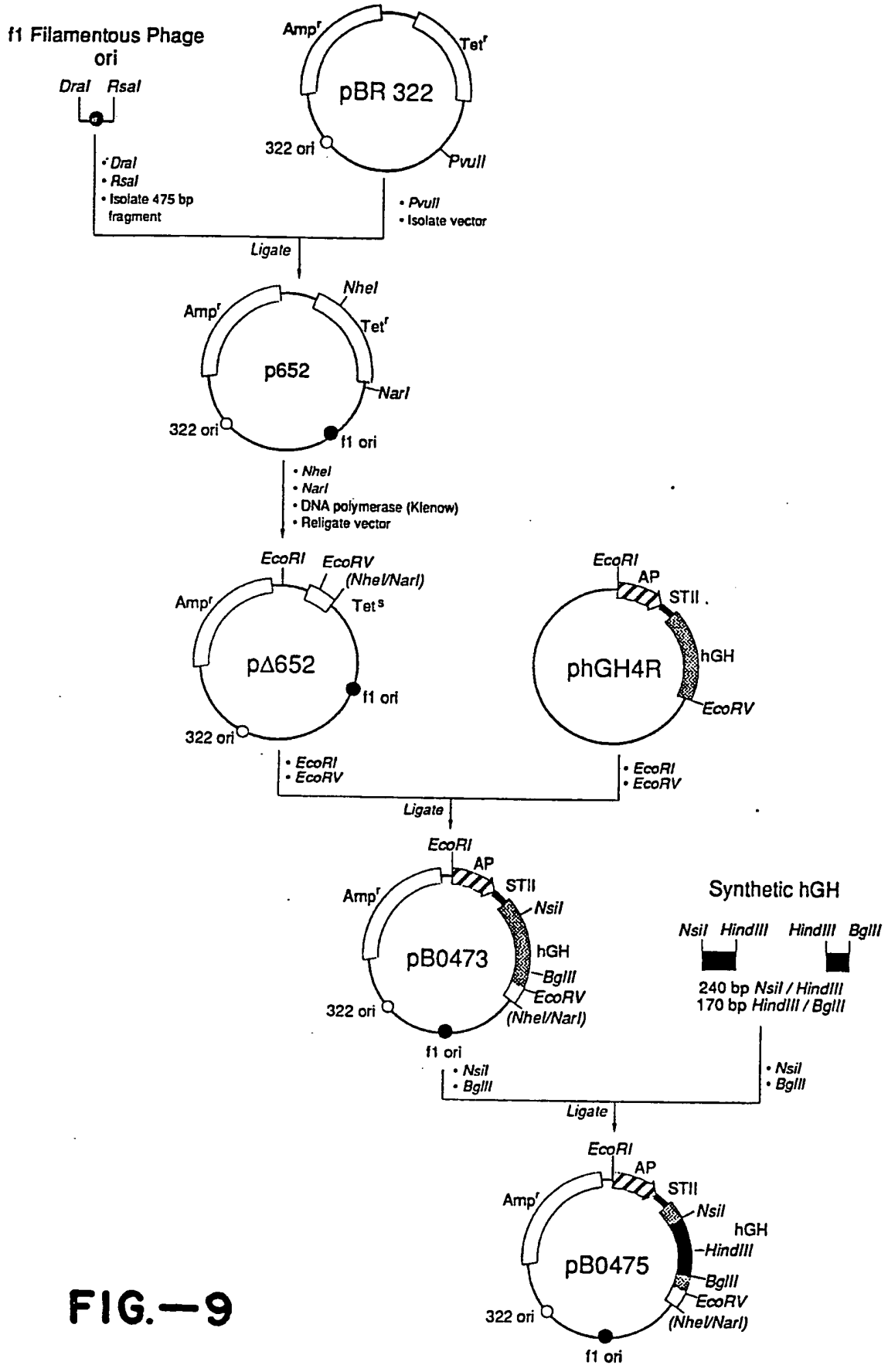


FIG.—9

SUBSTITUTE SHEET

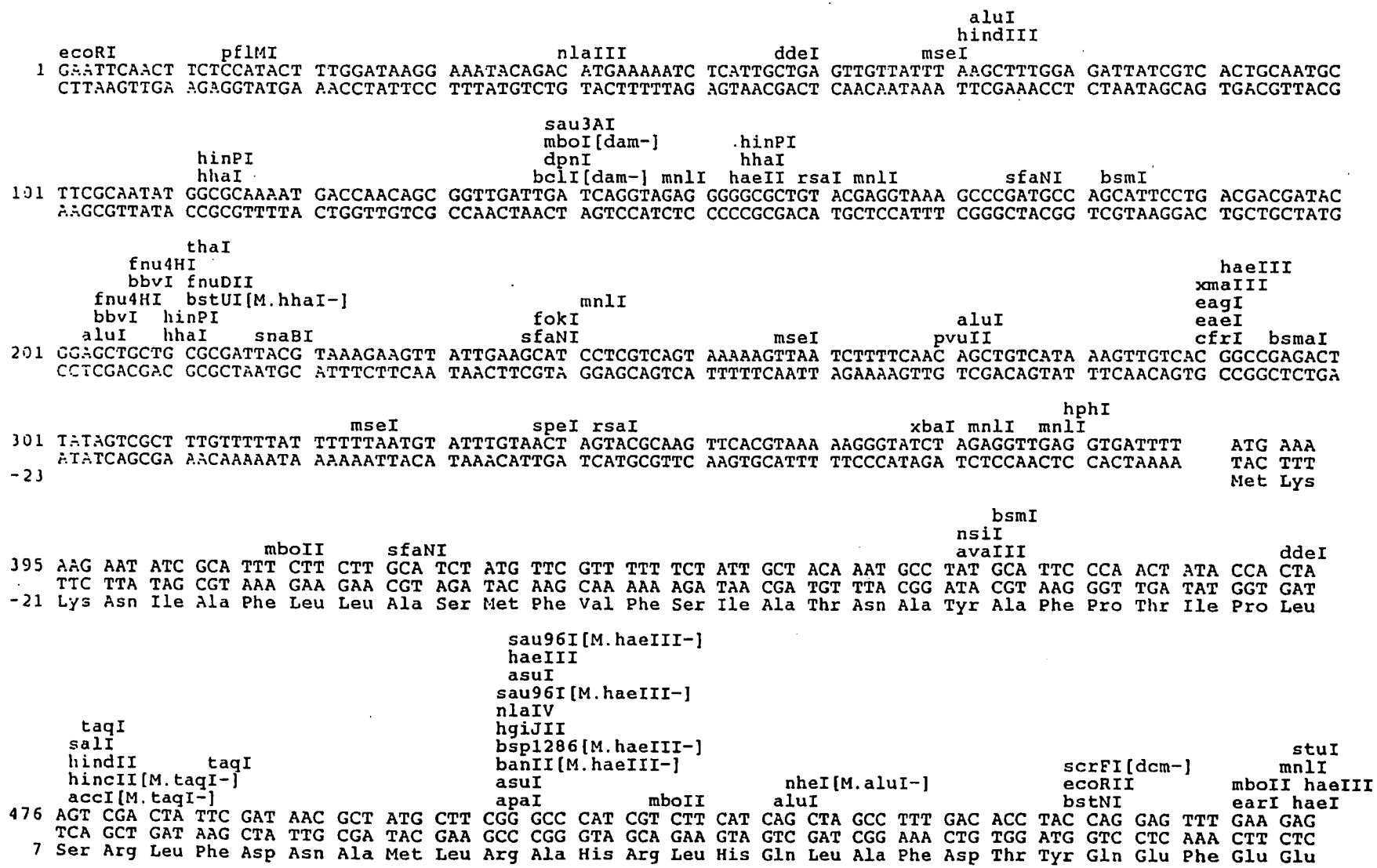


FIG.—10A

SUBSTITUTE SHEET

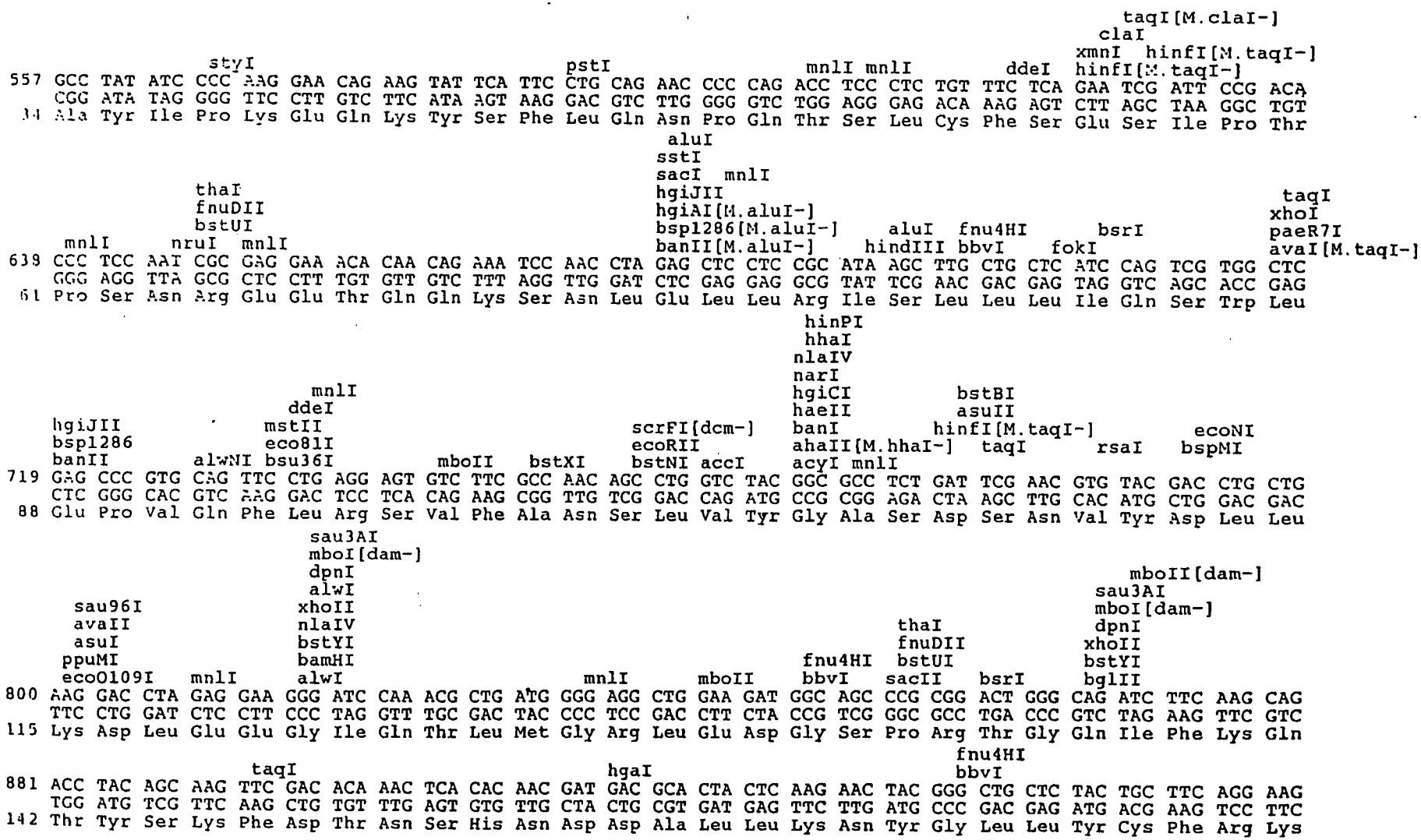


FIG.—10B

SUBSTITUTE SHEET

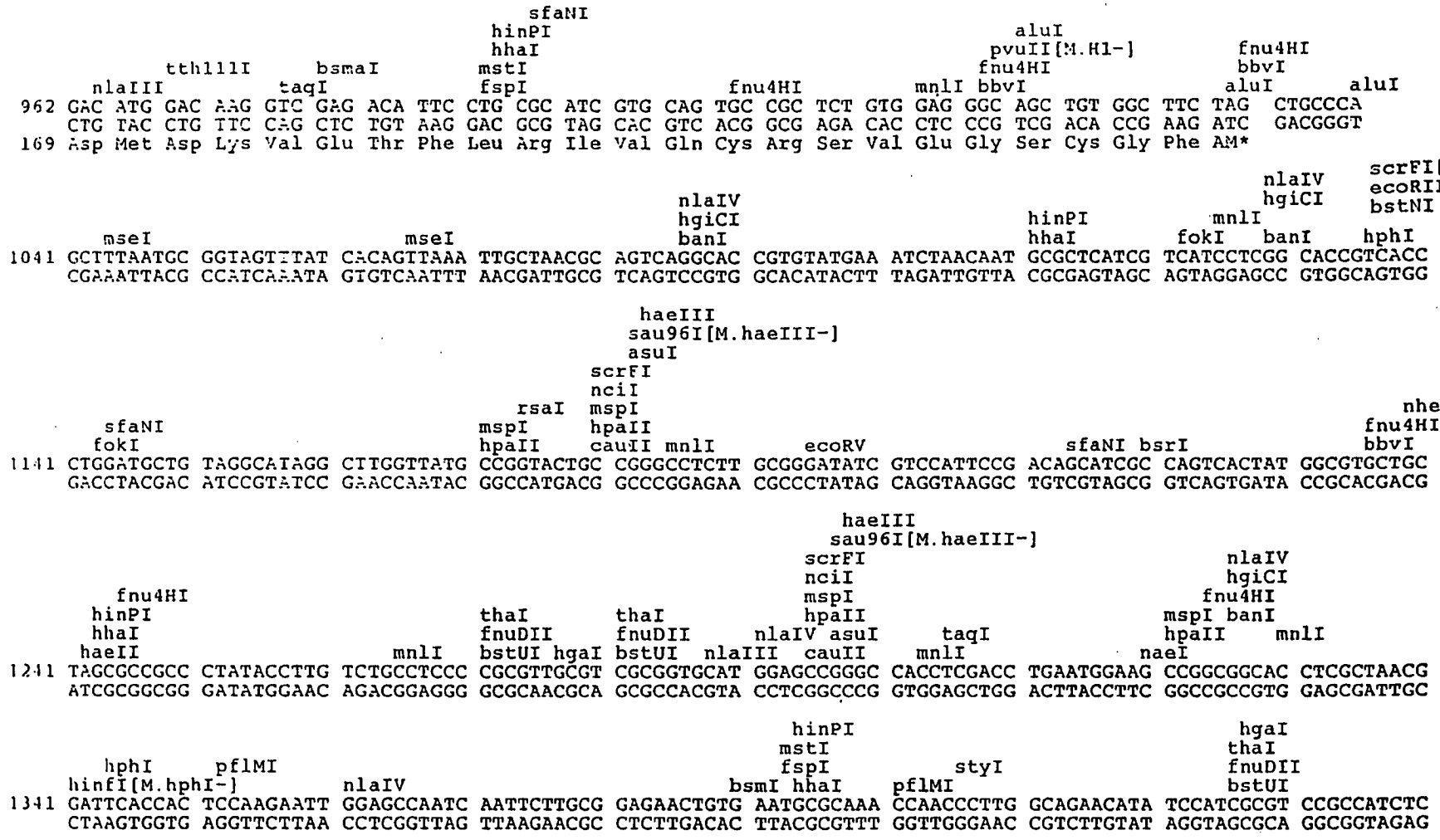


FIG.—10C

```
                                                  haeIII
                                                 haeI                                       scrFI
                                              scrFI[dcm-]                                   nciI
                                              ecoRII                                        cauII
                                              bstNI                                     sau96I
                     hinPI                 sau96I[dcm-]                                 nlaIV
                     hhaI                  avaII[dcm-]          nlaIII                  avaII
                  fnu4HI                   asuI  eaeI        hinPI     hgiAI            asuI mspI
          fnu4HI thaI                     ppuMI  cfrI        hhaI  sau3AI              ppuMI hpaII
       fnu4HI    fnuDII     avaI fnu4HI   nlaIV  balI[dcm-] mstI   mboI[dam-]          eco0109I
       bbvI      bstUI sfaNI      bbvI    eco0109I[dcm-]    fspI   dpnI bsp1286       mnlI
1441 CAGCAGCCGC ACGCGGCGCA TCTCGGGCAG CGTTGGGTCC TGGCCACGGG TGCGCATGAT CGTGCTCCTG TCGTTGAGGA CCCGGCTAGG CTGGCGGGGT
     GTCGTCGGCG TGCGCCGCGT AGAGCCCGTC GCAACCCAGG ACCGGTGCCC ACGCGTACTA GCACGAGGAC AGCAACTCCT GGGCCGATCC GACCGCCCCA

                                         thaI                   fnu4HI
                                         fnuDII                 bbvI
                               hphI      bstUI               fnu4HI
           bsrI         hinfI[M.hphI-]                       bbvI                   ddeI        nlaIII     mboII
1541 TGCCTTACTG GTTAGCAGAA TGAATCACCG ATACGCGAGC GAACGTGAAG CGACTGCTGC TGCAAAACGT CTGCGACCTG AGCAACAACA TGAATGGTCT
     ACGGAATGAC CAATCGTCTT ACTTAGTGGC TATGCGCTCG CTTGCACTTC GCTGACGACG ACGTTTTGCA GACGCTGGAC TCGTTGTTGT ACTTACCAGA

                                                                           sau3AI
                                                                           mboI[dam-]
                                                                           dpnI
                                                                          xhoII
                                                                          bstYI
                                                                          alwI
                                                                       mspI
                                      thaI        hinPI                hpaII            fnu4HI
                                      fnuDII      hhaI                bspMII       sfaNI
                                      bstUI      haeII                accIII    sfaNI   fokI bbvI
1641 TCGGTTTCCG TGTTTCGTAA AGTCTGGAAA CGCGGAAGTC AGCGCCCTGC ACCATTATGT TCCGGATCTG CATCGCAGGA TGCTGCTGGC TACCCTGTGG
     AGCCAAAGGC ACAAAGCATT TCAGACCTTT GCGCCTTCAG TCGCGGGACG TGGTAATACA AGGCCTAGAC GTAGCGTCCT ACGACGACCG ATGGGACACC

                                                                  sau96I
                               hinPI                              nlaIV      fokI
                               hhaI                               avaII     sfaNI
                      mseI     haeII      ddeI               asuI   fnu4HI    bsrI     mnlI
1741 AACACCTACA TCTGTATTAA CGAAGCGCTG GCATTGACCC TGAGTGATTT TTCTCTGGTC CCGCCGCATC CATACCGCCA GTTGTTTACC CTCACAACGT
     TTGTGGATGT AGACATAATT GCTTCGCGAC CGTAACTGGG ACTCACTAAA AAGAGACCAG GGCGGCGTAG GTATGGCGGT CAACAAATGG GAGTGTTGCA

             scrFI
             nciI
             mspI nspCIx                                mnlI
             hpaII                                   fokI
      bsrI   cauII nlaIII                           sfaNI                              nlaIII
1841 TCCAGTAACC GGGCATGTTC ATCATCAGTA ACCCGTATCG TGAGCATCCT CTCTCGTTTC ATCGGTATCA TTACCCCCAT GAACAGAAAT TCCCCCTTAC
     AGGTCATTGG CCCGTACAAG TAGTAGTCAT TGGGCATAGC ACTCGTAGGA GAGAGCAAAG TAGCCATAGT AATGGGGGTA CTTGTCTTTA AGGGGGAATG
```

FIG.—10D


sau96I[M.haeIII-]
haeIII
asuI
sfaNI
mnlI
mseI nlaIII
mseI
aluI
1941 ACGGAGGCAT CAAGTGACCA AACAGGAAAA AACCGCCCTT AACATGGCCC GCTTTATCAG AAGCCAGACA TTAACGCTTC TGGAGAAACT CAACGAGCTG
TGCCTCCGTA GTTCACTGGT TTGTCCTTTT TTGGCGGGAA TTGTACCGGG CGAAATAGTC TTCGGTCTGT AATTGCGAAG ACCTCTTTGA GTTGCTCGAC
mspI[M.bamHI-]
hpaII
bspMII
accIII
sau3AI
mboI[dam-]
dpnI
alwI
xhoII
nlaIV
bstYI
thaI
fnuDII
bstUI
xmnI
bamHI[M.mspI-]
sspI
hgaI fokI
hinfI
aluI
alwI
mseI
mseI
2041 GACGCGGATG AACAGGCAGA CATCTGTGAA TCGCTTCACG ACCACGCTGA TGAGCTTTAC CGCAGGATCC GGAAATTGTA AACGTTAATA TTTTGTTAAA
CTGCGCCTAC TTGTCCGTCT GTAGACACTT AGCGAAGTGC TGGTGCGACT ACTCGAAATG GCGTCCTAGG CCTTTAACAT TTGCAATTAT AAAACAATTT
mseI
thaI
fnuDII
bstUI
mseI
aluI
mseI
haeIII
2141 ATTCGCGTTA AATTTTTGTT AAATCAGCTC ATTTTTTAAC CAATAGGCCG AAATCGGCAA AATCCCTTAT AAATCAAAAG AATAGACCGA GATAGGGTTG
TAAGCGCAAT TTAAAAACAA TTTAGTCGAG TAAAAAATTG GTTATCCGGC TTTAGCCGTT TTAGGGAATA TTTAGTTTTC TTATCTGGCT CTATCCCAAC
sau96I[M.haeIII-]
haeIII
asuI draIII
pleI
pleI
bsrI
hinfI
mseI
hinfI
2241 AGTGTTGTTC CAGTTTGGAA CAAGAGTCCA CTATTAAAGA ACGTGGACTC CAACGTCAAA GGGCGAAAAA CCGTCTATCA GGGCTATGGC CCACTACGTG
TCACAACAAG GTCAAACCTT GTTCTCAGGT GATAATTTCT TGCACCTGAG GTTGCAGTTT CCCGCTTTTT GGCAGATAGT CCCGATACCG GGTGATGCAC
nlaIV
hgiCI
hgiJII
bsp1286
mspI
mnlI
banII
hpaII
hphI
taqI banI
nlaIV
nlaIV
aluI
naeI
2341 AACCATCACC CTAATCAAGT TTTTTGGGGT CGAGGTGCCG TAAAGCACTA AATCGGAACC CTAAAGGGAG CCCCCGATTT AGAGCTTGAC GGGGAAAGCC
TTGGTAGTGG GATTAGTTCA AAAAACCCCA GCTCCACGGC ATTTCGTGAT TTAGCCTTGG GATTTCCCTC GGGGGCTAAA TCTCGAACTG CCCCTTTCGG

FIG.—10E


thaI
fnuDII
bstUI[M.hhaI-]
thaI
fnuDII
hinPI
hinPI
hhaI
hhaI
bstUI[M.hha
fnu4HI
mboII
haeII
haeII
bbvI
fnu4HI
2441 GGCGAACGTG GCGAGAAAGG AAGGGAAGAA AGCGAAAGGA GCGGGCGCTA GGGCGCTGGC AAGTGTAGCG GTCACGCTGC GCGTAACCAC CACACCCGCC
CCGCTTGCAC CGCTCTTTCC TTCCCTTCTT TCGCTTTCCT CGCCCGCGAT CCCGCGACCG TTCACATCGC CAGTGCGACG CGCATTGGTG GTGTGGGCGG
sau3AI
mboI[dam-]
dpnI
alwI
xhoII
nlaIV
thaI
bstYI
fnuDII
bspMII
bstUI[M.hhaI-]
hgaI
bamHI[M.mspI-]
scrFI
thaI mspI[M.bamHI-]
hinPI
fnu4HI mspI
fnuDII
alwI
thaI
bbvI
nciI bsmaI
mseI
fnu4HI
bstUI[M.hhaI-]
fnuDII
nlaIII
cauII
hinPI
hinPI
hinPI hpaII
bstUI[M.hhaI-]
nspCIx aluI hpaII
hhaI
hhaI
hhaI accIII
mnlI hhaI
hphI
hphI
mnlI
2541 GCGCTTAATG CGCCGCTACA GGGCGCGTCC GGATCCTGCC TCGCGCGTTT CGGTGATGAC GGTGAAAACC TCTGACACAT GCAGCTCCCG GAGACGGTCA
CGCGAATTAC GCGGCGATGT CCCGCGCAGG CCTAGGACGG AGCGCGCAAA GCCACTACTG CCACTTTTGG AGACTGTGTA CGTCGAGGGC CTCTGCCAGT
scrFI
hgaI
nciI
thaI
mspI
fnuDII
fnu4HI
hpaII
bstUI[M.hhaI-]
bbvI
bsrI
sfaNI
hinPI
hinPI
tthlIII
aluI
fokI
cauII
hhaI
hhaI
nlaIII
2641 CAGCTTGTCT GTAAGCGGAT GCCGGGAGCA GACAAGCCCG TCAGGGCGCG TCAGCGGGTG TTGGCGGGTG TCGGGGCGCA GCCATGACCC AGTCACGTAG
GTCGAACAGA CATTCGCCTA CGGCCCTCGT CTGTTCGGGC AGTCCCGCGC AGTCGCCCAC AACCGCCCAC AGCCCCGCGT CGGTACTGGG TCAGTGCATC
hgiAI
bsrI
sfaNI
ddeI
bsp1286
accI
mseI
fnu4HI
rsaI
apaLI
ndeI
sfaNI
2741 CGATAGCGGA GTGTATACTG GCTTAACTAT GCGGCATCAG AGCAGATTGT ACTGAGAGTG CACCATATGC GGTGTGAAAT ACCGCACAGA TGCGTAAGGA
GCTATCGCCT CACATATGAC CGAATTGATA CGCCGTAGTC TCGTCTAACA TGACTCTCAC GTGGTATACG CCACACTTTA TGGCGTGTCT ACGCATTCCT
earI
hinPI
hinPI
fnu4HI
fnu4HI
hhaI
pleI bbvI
fnu4HI
sfaNI
haeII
mboII
mnlI
hinfI
hhaI
bbvI
aluI
2841 GAAAATACCG CATCAGGCGC TCTTCCGCTT CCTCGCTCAC TGACTCGCTG CGCTCGGTCG TTCGGCTGCG GCGAGCGGTA TCAGCTCACT CAAAGGCGGT
CTTTTATGGC GTAGTCCGCG AGAAGGCGAA GGAGCGAGTG ACTGAGCGAC GCGAGCCAGC AAGCCGACGC CGCTCGCCAT AGTCGAGTGA GTTTCCGCCA

FIG.—10F

FIG.—10G

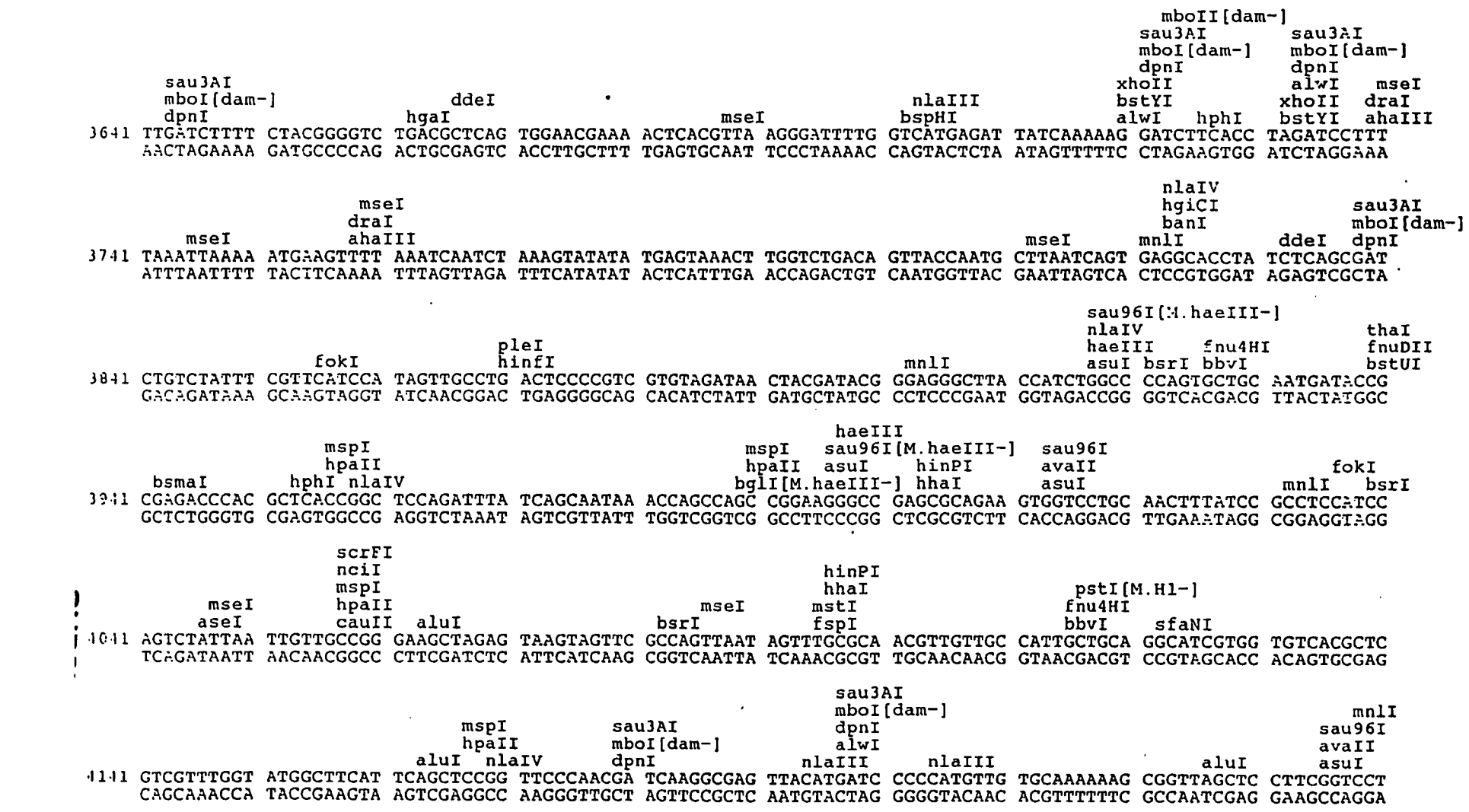

mboII[dam-]
sau3AI
mboI[dam-]
dpnI
sau3AI
mboI[dam-]
dpnI
sau3AI
mboI[dam-]
dpnI
xhoII
alwI
mseI
ddeI
nlaIII
bstYI
xhoII
draI
hgaI
mseI
bspHI
alwI
hphI
bstYI
ahaIII
3641 TTGATCTTTT CTACGGGGTC TGACGCTCAG TGGAACGAAA ACTCACGTTA AGGGATTTTG GTCATGAGAT TATCAAAAAG GATCTTCACC TAGATCCTTT
AACTAGAAAA GATGCCCCAG ACTGCGAGTC ACCTTGCTTT TGAGTGCAAT TCCCTAAAAC CAGTACTCTA ATAGTTTTTC CTAGAAGTGG ATCTAGGAAA
nlaIV
mseI
hgiCI
sau3AI
draI
banI
mboI[dam-]
mseI
ahaIII
mseI
mnlI
ddeI
dpnI
3741 TAAATTAAAA ATGAAGTTTT AAATCAATCT AAAGTATATA TGAGTAAACT TGGTCTGACA GTTACCAATG CTTAATCAGT GAGGCACCTA TCTCAGCGAT
ATTTAATTTT TACTTCAAAA TTTAGTTAGA TTTCATATAT ACTCATTTGA ACCAGACTGT CAATGGTTAC GAATTAGTCA CTCCGTGGAT AGAGTCGCTA
sau96I[M.haeIII-]
nlaIV
thaI
haeIII
fnu4HI
fnuDII
pleI
fokI
hinfI
mnlI
asuI
bsrI
bbvI
bstUI
3841 CTGTCTATTT CGTTCATCCA TAGTTGCCTG ACTCCCCGTC GTGTAGATAA CTACGATACG GGAGGGCTTA CCATCTGGCC CCAGTGCTGC AATGATACCG
GACAGATAAA GCAAGTAGGT ATCAACGGAC TGAGGGGCAG CACATCTATT GATGCTATGC CCTCCCGAAT GGTAGACCGG GGTCACGACG TTACTATGGC
haeIII
mspI
mspI
sau96I[M.haeIII-]
sau96I
hpaII
hpaII
asuI
hinPI
avaII
fokI
bsmaI
hphI
nlaIV
bglI[M.haeIII-]
hhaI
asuI
mnlI
bsrI
3941 CGAGACCCAC GCTCACCGGC TCCAGATTTA TCAGCAATAA ACCAGCCAGC CGGAAGGGCC GAGCGCAGAA GTGGTCCTGC AACTTTATCC GCCTCCATCC
GCTCTGGGTG CGAGTGGCCG AGGTCTAAAT AGTCGTTATT TGGTCGGTCG GCCTTCCCGG CTCGCGTCTT CACCAGGACG TTGAAATAGG CGGAGGTAGG
scrFI
nciI
hinPI
mspI
hhaI
pstI[M.HI-]
mseI
hpaII
mseI
mstI
fnu4HI
aseI
cauII
aluI
bsrI
fspI
bbvI
sfaNI
4041 AGTCTATTAA TTGTTGCCGG GAAGCTAGAG TAAGTAGTTC GCCAGTTAAT AGTTTGCGCA ACGTTGTTGC CATTGCTGCA GGCATCGTGG TGTCACGCTC
TCAGATAATT AACAACGGCC CTTCGATCTC ATTCATCAAG CGGTCAATTA TCAAACGCGT TGCAACAACG GTAACGACGT CCGTAGCACC ACAGTGCGAG
sau3AI
mboI[dam-]
mnlI
mspI
sau3AI
dpnI
sau96I
hpaII
mboI[dam-]
alwI
avaII
aluI
nlaIV
dpnI
nlaIII
nlaIII
aluI
asuI
4141 GTCGTTTGGT ATGGCTTCAT TCAGCTCCGG TTCCCAACGA TCAAGGCGAG TTACATGATC CCCCATGTTG TGCAAAAAAG CGGTTAGCTC CTTCGGTCCT
CAGCAAACCA TACCGAAGTA AGTCGAGGCC AAGGGTTGCT AGTTCCGCTC AATGTACTAG GGGGTACAAC ACGTTTTTTC GCCAATCGAG GAAGCCAGGA

FIG.—10H

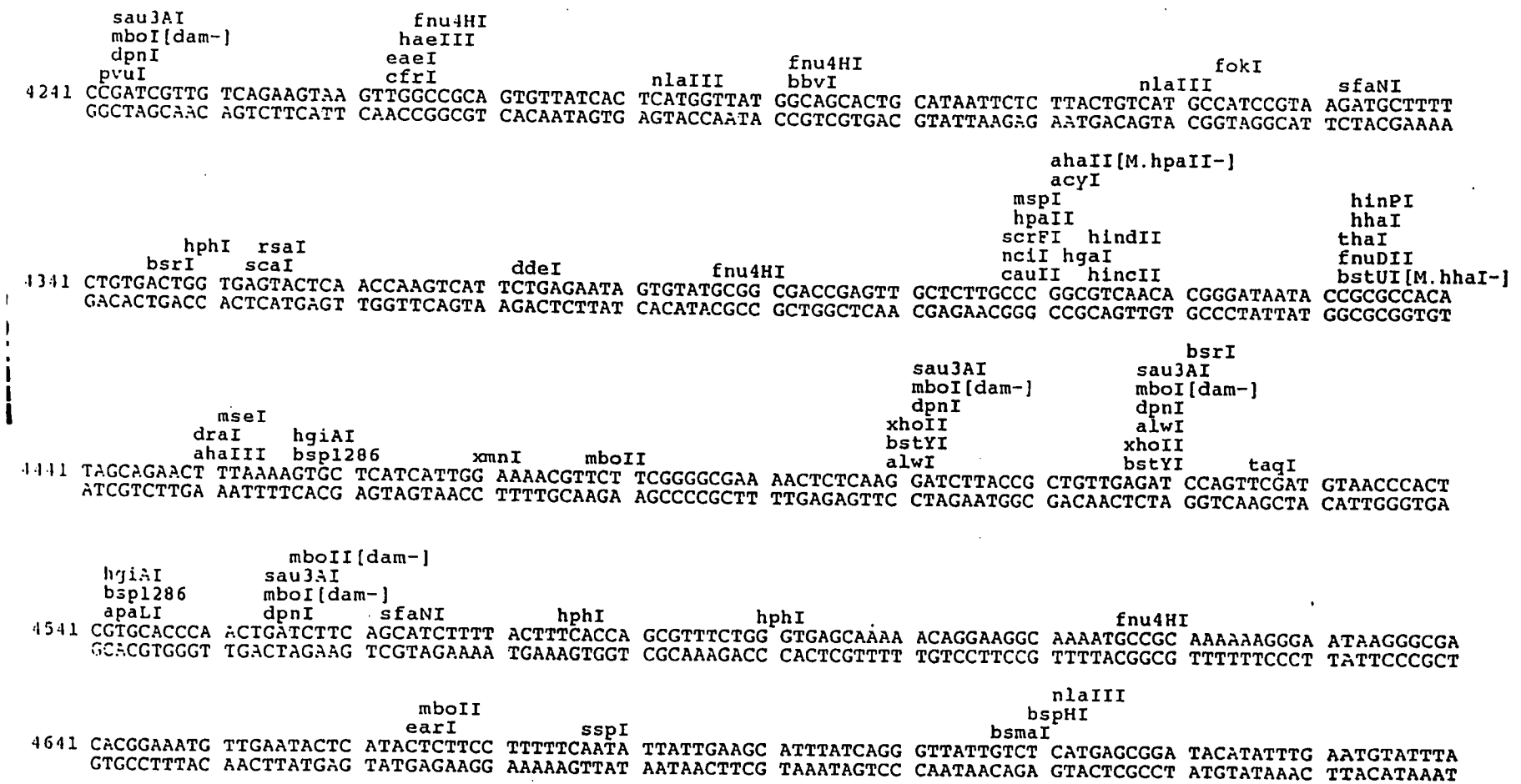

sau3AI
mboI[dam-]
dpnI
pvuI
fnu4HI
haeIII
eaeI
cfrI
nlaIII
fnu4HI
bbvI
fokI
nlaIII
sfaNI
4241 CCGATCGTTG TCAGAAGTAA GTTGGCCGCA GTGTTATCAC TCATGGTTAT GGCAGCACTG CATAATTCTC TTACTGTCAT GCCATCCGTA AGATGCTTTT
GGCTAGCAAC AGTCTTCATT CAACCGGCGT CACAATAGTG AGTACCAATA CCGTCGTGAC GTATTAAGAG AATGACAGTA CGGTAGGCAT TCTACGAAAA
ahaII[M.hpaII-]
acyI
mspI
hpaII
hinPI
hhaI
hphI
rsaI
bsrI
scaI
ddeI
fnu4HI
scrFI
hindII
ncil
hgaI
cauII
hincII
thaI
fnuDII
bstUI[M.hhaI-]
4341 CTGTGACTGG TGAGTACTCA ACCAAGTCAT TCTGAGAATA GTGTATGCGG CGACCGAGTT GCTCTTGCCC GGCGTCAACA CGGGATAATA CCGCGCCACA
GACACTGACC ACTCATGAGT TGGTTCAGTA AGACTCTTAT CACATACGCC GCTGGCTCAA CGAGAACGGG CCGCAGTTGT GCCCTATTAT GGCGCGGTGT
bsrI
sau3AI
mboI[dam-]
dpnI
sau3AI
mboI[dam-]
dpnI
alwI
xhoII
bstYI
alwI
xhoII
bstYI
taqI
mseI
draI
ahaIII
hgiAI
bspl286
xmnI
mboII
4441 TAGCAGAACT TTAAAAGTGC TCATCATTGG AAAACGTTCT TCGGGGCGAA AACTCTCAAG GATCTTACCG CTGTTGAGAT CCAGTTCGAT GTAACCCACT
ATCGTCTTGA AATTTTCACG AGTAGTAACC TTTTGCAAGA AGCCCCGCTT TTGAGAGTTC CTAGAATGGC GACAACTCTA GGTCAAGCTA CATTGGGTGA
mboII[dam-]
hgiAI
bspl286
apaLI
sau3AI
mboI[dam-]
dpnI
sfaNI
hphI
hphI
fnu4HI
4541 CGTGCACCCA ACTGATCTTC AGCATCTTTT ACTTTCACCA GCGTTTCTGG GTGAGCAAAA ACAGGAAGGC AAAATGCCGC AAAAAAGGGA ATAAGGGCGA
GCACGTGGGT TGACTAGAAG TCGTAGAAAA TGAAAGTGGT CGCAAAGACC CACTCGTTTT TGTCCTTCCG TTTTACGGCG TTTTTTCCCT TATTCCCGCT
nlaIII
bspHI
bsmaI
mboII
earI
sspI
4641 CACGGAAATG TTGAATACTC ATACTCTTCC TTTTTCAATA TTATTGAAGC ATTTATCAGG GTTATTGTCT CATGAGCGGA TACATATTTG AATGTATTTA
GTGCCTTTAC AACTTATGAG TATGAGAAGG AAAAAGTTAT AATAACTTCG TAAATAGTCC CAATAACAGA GTACTCGCCT ATGTATAAAC TTACATAAAT

FIG.—101

```
                                  hinPI
                                  hhaI
                                 thaI                              ahaII
                                 fnuDII                            acyI ddeI                 nlaIII
                          nlaIV bstUI[M.hhaI-]                     aatII                     bspHI    mseI
4741 GAAAAATAAA CAAATAGGGG TTCCGCGCAC ATTTCCCCGA AAAGTGCCAC CTGACGTCTA AGAAACCATT ATTATCATGA CATTAACCTA TAAAAATAGG
     CTTTTTATTT GTTTATCCCC AAGGCGCGTG TAAAGGGGCT TTTCACGGTG GACTGCAGAT TCTTTGGTAA TAATAGTACT GTAATTGGAT ATTTTTATCC

                    sau96I[M.haeIII-]
                    haeIII
                    asuI
                  eco0109I
                 mnlI          mboII
4841 CGTATCACGA GGCCCTTTCG TCTTCAA
     GCATAGTGCT CCGGGAAAGC AGAAGTT
```

length: 4867

```
aarII(GACGTC):          4793
accI(GTMKAC):           477[M.taqI-] 761 2753
accIII(TCCGGA):         1701 2108 2568
acyI(GRCGYC):           767 4411 4793
ahaII(GRCGYC):          767[M.hhaI-] 4411[M.hpaII-] 4793
ahaIII(TTTAAA):         3739 3758 4450
alul(AGCT):             72 203 271 522 678 692 1019 1032 1040 2036 2093 2166 2423 2623 2642 2923 3149
                        3239 3285 3542 4063 4163 4226
alwI(GGATC):            816 817 1704 2105 2106 2571 2572 3549 3623 3635 3720 3733 4197 4500 4518
alwNI(CAGNNNCTG):       728 3393
apaI(GGGCCC):           504
apaLI(GTGCAC):          2798 3296 4542
aseI(ATTAAT):           4046
asuI(GGNCC):            504 505 802 1182 1297 1476 1518 1797 1986 2328 3917 3996 4013 4235 4851
asuII(TTCGAA):          778
avaI(CYCGRG):           716[M.taqI-] 1462
avaII(GGWCC):           802 1476[dcm-] 1518 1797 4013 4235
avaIII(ATGCAT):         453
balI(TGGCCA):           1481[dcm-]
bamHI(GGATCC):          816 2105[M.mspI-] 2571[M.mspI-]
banI(GGYRCC):           767 1086 1129 1326 2374 3823
banII(GRGCYC):          504[M.haeIII-] 677[M.aluI-] 719 2408
bbvI(GCAGC):            204 207 697 849 940 1017 1033 1236 1443 1467 1596 1599 1722 2516 2621 2718 2887
                        2905 3324 3389 3392 3598 3926 4115 4292
bclI[dam-](TGATCA):     138
```

FIG.—10J

```
bglI(GCCNNNNNGGC):      3989[M.haeIII-]
bglII(AGATCT):          867
bsmI(GAATGC):           182 455 1390
bsmAI(GTCTC):           295 977 2631 3942 4707
bspI286(GDGCHC):        504[M.haeIII-] 677[M.aluI-] 719 1502 2408 2798 3296 4457 4542
bspHI(TCATGA):          3702 4710 4815
bspMI(ACCTGC):          792
bspMII(TCCGGA):         1701 2108 2568
bstI(ACTGG):            706 860 1220 1547 1818 1842 2250 2729 2757 3385 3398 3515 3921 4039 4082 4346
                        4521
bstBI(TTCGAA):          778
bstNI(CCWGG):           541 757 1140 1479 3009 3130 3143
bstUI(CGCG):            211[M.hhaI-] 647 855 1271 1281 1426 1452 1574 1671 2043 2144 2520[M.hhaI-] 2540[M.hhaI-]
                        2564[M.hhaI-] 2582[M.hhaI-] 2584[M.hhaI-] 2687[M.hhaI-] 3028 3609[M.hhaI-] 3939
                        4432[M.hhaI-] 4764[M.hhaI-]
bstXI(CCANNNNNNTGG):    750
bstYI(RGATCY):          816 867 1704 2105 2571 3623 3634 3720 3732 4500 4517
bsu36I(CCTNAGG):        733
cauII(CCSGG):           1180 1295 1521 1849 2627 2662 3361 4057 4408
cfrI(YGGCCR):           290 1481 4263
claI(ATCGAT):           625
ddeI(CTNAG):            57 473 619 734 1618 1780 2792 3257 3666 3832 4372 4798
dpnI(GATC):             139 817 868 1498 1705 2106 2572 3549 3624 3635 3643 3721 3733 3838 4179 4197
                        4243 4501 4518 4554
draI(TTTAAA):           3739 3758 4450
draIII(CACNNNGTG):      2332
eaeI(YGGCCR):           290 1481 4263
eagI(CGGCCG):           290
earI(CTCTTC):           551 2860 4664
eco81I(CCTNAGG):        733
ecoNI(CCTNNNNNAGG):     793
eco0109I(RGGNCCY):      801 1475[dcm-] 1517 4850
ecoRI(GAATTC):          1
ecoRII(CCWGG):          541 757 1140 1479 3009 3130 3143
ecoRV(GATATC):          1195
fnu4HI(GCNGC):          204 207 697 849 940 1002 1017 1033 1236 1245 1324 1443 1446 1453 1467 1596 1599
                        1722 1803 2516 2538 2552 2621 2718 2771 2887 2905 2908 3026 3181 3324 3389 3392
                        3598 3926 4115 4265 4292 4387 4616
fnuDII(CGCG):           211 647 855 1271 1281 1426 1452 1574 1671 2043 2144 2520 2540 2564 2582 2584
                        2687 3028 3609 3939 4432 4764
fokI(GGATG):            238 703 1122 1143 1718 1807 1885 2046 2657 3855 4036 4323
fspI(TGCGCA):           987 1393 1491 4095
haeI(WGGCCW):           555 1481 2995 3006 3458
haeII(RGCGCY):          153 767 1242 1681 1764 2484 2492 2856 3226
haeIII(GGCC):           291 505 556 1183 1298 1482 1986 2186 2328 2996 3007 3025 3459 3917 3997 4264
                        4851
```

FIG.—10K

```
hgaI(GACGC):          917 1277 1427 2041 2565 2688 3084 3662 4412
hgiAI(GWGCWC):        677[M.aluI-] 1502 2798 3296 4457 4542
hgiCI(GGYRCC):        767 1086 1129 1326 2374 3823
hgiJII(GRGCYC):       504 677 719 2408
hhaI(GCGC):           112 154 210 768 988 1111 1243 1394 1456 1492 1682 1765 2485 2493 2519 2541 2550
                      2563 2583 2686 2716 2857 2890 3160 3227 3327 3501 3610 4003 4096 4433 4765
hinPI(GCGC):          112 154 210 768 988 1111 1243 1394 1456 1492 1682 1765 2485 2493 2519 2541 2550
                      2563 2583 2686 2716 2857 2890 3160 3227 3327 3501 3610 4003 4096 4433 4765
hincII(GTYRAC):       477[M.taqI-] 4414
hindII(GTYRAC):       477 4414

hindIII(AAGCTT):      71 691
hinfI(GANTC):         623[M.taqI-] 628[M.taqI-] 776[M.taqI-] 1341[M.hphI-] 1562[M.hphI-] 2068 2264
                      2286 2882 2957 3353 3870
hpaII(CCGG):          1171 1180 1295 1321 1522 1702 1849 2109 2439 2569 2628 2662 3189 3336 3362 3552
                      3956 3990 4057 4167 4409
hphI(GGTGA):          380 1136 1344 1565 2346 2592 2601 3726 3953 4349 4575 4590
mboII(GAAGA):         409 514 551 744 842 870[dam-] 1638 2465 2861 3632[dam-] 3723[dam-] 4478 4556[dam-]
                      4665 4861
mboI[dam-](GATC):     139 817 868 1498 1705 2106 2572 3549 3624 3635 3643 3721 3733 3838 4179 4197
                      4243 4501 4518 4554
mnlI(CCTC):           148 163 241 372 378 554 606 610 639 650 682 736 771 809 835 1013 1125 1185 1265
                      1303 1330 1516 1830 1888 1944 2372 2579 2609 2871 3097 3154 3421 3821 3902 4032
                      4238 4849
msel(TTAA):           69 257 324 1044 1066 1757 1979 2011 2125 2136 2148 2159 2176 2274 2545 2763
                      3688 3740 3745 3759 3812 4047 4086 4451 4823
mspI(CCGG):           1171 1180 1295 1321 1522 1702 1849 2109[M.bamHI-] 2439 2569[M.bamHI-] 2628 2662
                      3189 3336 3362 3552 3956 3990 4057 4167 4409
mstI(TGCGCA):         987 1393 1491 4095
mstII(CCTNAGG):       733
naeI(GCCGGC):         1320 2438
narI(GGCGCC):         767
ncil(CCSGG):          1180 1295 1521 1849 2627 2662 3361 4057 4408
ndeI(CATATG):         2804
nheI(GCTAGC):         523[M.aluI-] 1239
nlaIII(CATG):         40 964 1288 1495 1629 1854 1918 1983 2618 2723 2983 3703 4194 4204 4282 4318
                      4711 4816
nlaIV(GGNNCC):        504 767 816 1086 1129 1291 1326 1361 1475 1518 1797 2105 2374 2395 2407 2571
                      3012 3051 3823 3917 3958 4169 4759
nruI(TCGCGA):         646
nsiI(ATGCAT):         453
nspCIx(RCATGY):       1853 2617 2982
paeR7I(CTCGAG):       716
pflMI(CCANNNNNTGG):   14 1352 1401
pleI(GAGTC):          2264 2286 2882 3353 3870
ppuMI(RGGWCCY):       801 1475 1517
pstI(CTGCAG):         590 4116[M.H1-]
```

FIG.—10L

```
pvuI(CGATCG):           4242
pvuII(CAGCTG):          270 1018[M.H1-]
rsaI(GTAC):             159 342 787 1174 2789 4354
sacI(GAGCTC):           677
sacII(CCGCGG):          854
salI(GTCGAC):           477
sau3AI(GATC):           139 817 868 1498 1705 2106 2572 3549 3624 3635 3643 3721 3733 3838 4179 4197
                        4243 4501 4518 4554
sau96I(GGNCC):          504[M.haeIII-] 505[M.haeIII-] 802 1182[M.haeIII-] 1297[M.haeIII-] 1476[dcm-]
                        1518 1797 1986[M.haeIII-] 2328[M.haeIII-] 3917[M.haeIII-] 3996[M.haeIII-] 4013
                        4235 4851[M.haeIII-]
scaI(AGTACT):           4353
scrFI(CCSGG):           1180 1295 1521 1849 2627 2662 3361 4057 4408
scrFI[dcm-](CCWGG):     541 757 1140 1479 3009 3130 3143
sfaNI(GCATC):           175 237 416 990 1144 1214 1458 1710 1719 1806 1884 1947 2658 2774 2829 2850
                        3070 4122 4332 4562
snaBI(TACGTA):          217
speI(ACTAGT):           338
sspI(AATATT):           2127 4677
sstI(GAGCTC):           677
stuI(AGGCCT):           555
styI(CCWWGG):           567 1406
taqI(TCGA):             478 486 626[M.claI-] 717 779 894 975 1305 2370 3082 4526
thaI(CGCG):             211 647 855 1271 1281 1426 1452 1574 1671 2043 2144 2520 2540 2564 2582 2584
                        2687 3028 3609 3939 4432 4764
tth111I(GACNNNGTC):     968 2726
xbaI(TCTAGA):           368
xhoI(CTCGAG):           716
xhoII(RGATCY):          816 867 1704 2105 2571 3623 3634 3720 3732 4500 4517
xmaIII(CGGCCG):         290
xmnI(GAANNNNTTC):       623 2068 4470
not found:
aflII(CTTAAG), asp718(GGTACC), avrII(CCTAGG), bssHII(GCGCGC), bstEII(GGTNACC), espI(GCTNAGC), hpaI(GTTAAC),
kpnI(GGTACC), mluI(ACGCGT), ncoI(CCATGG), notI(GCGGCCGC), rsrII(CGGWCCG), sfiI(GGCCNNNNNGGCC), smaI(CCCGGG),
sphI(GCATGC), xmaI(CCCGGG)
```

FIG.—10M

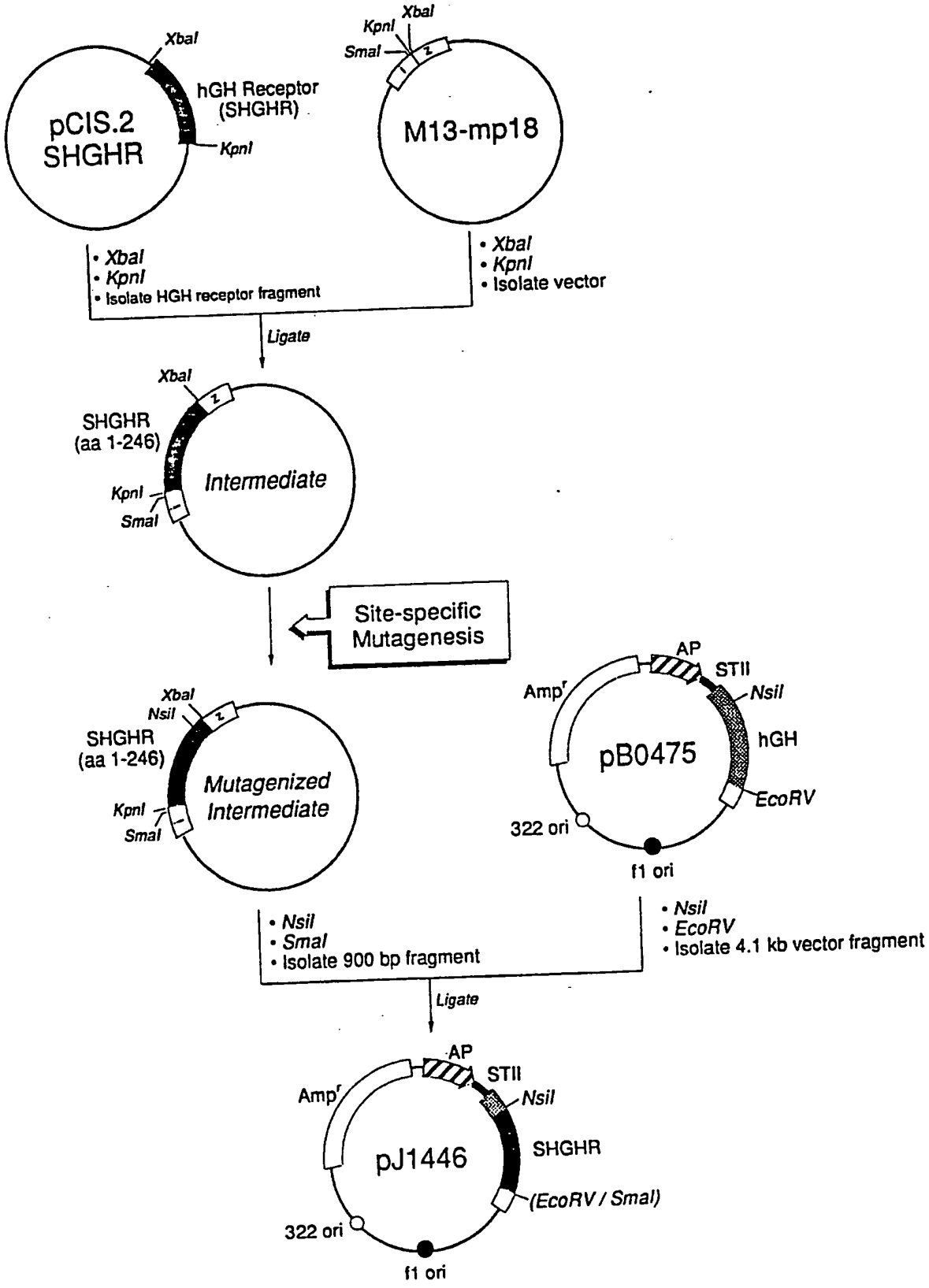


FIG.—11

SUBSTITUTE SHEET

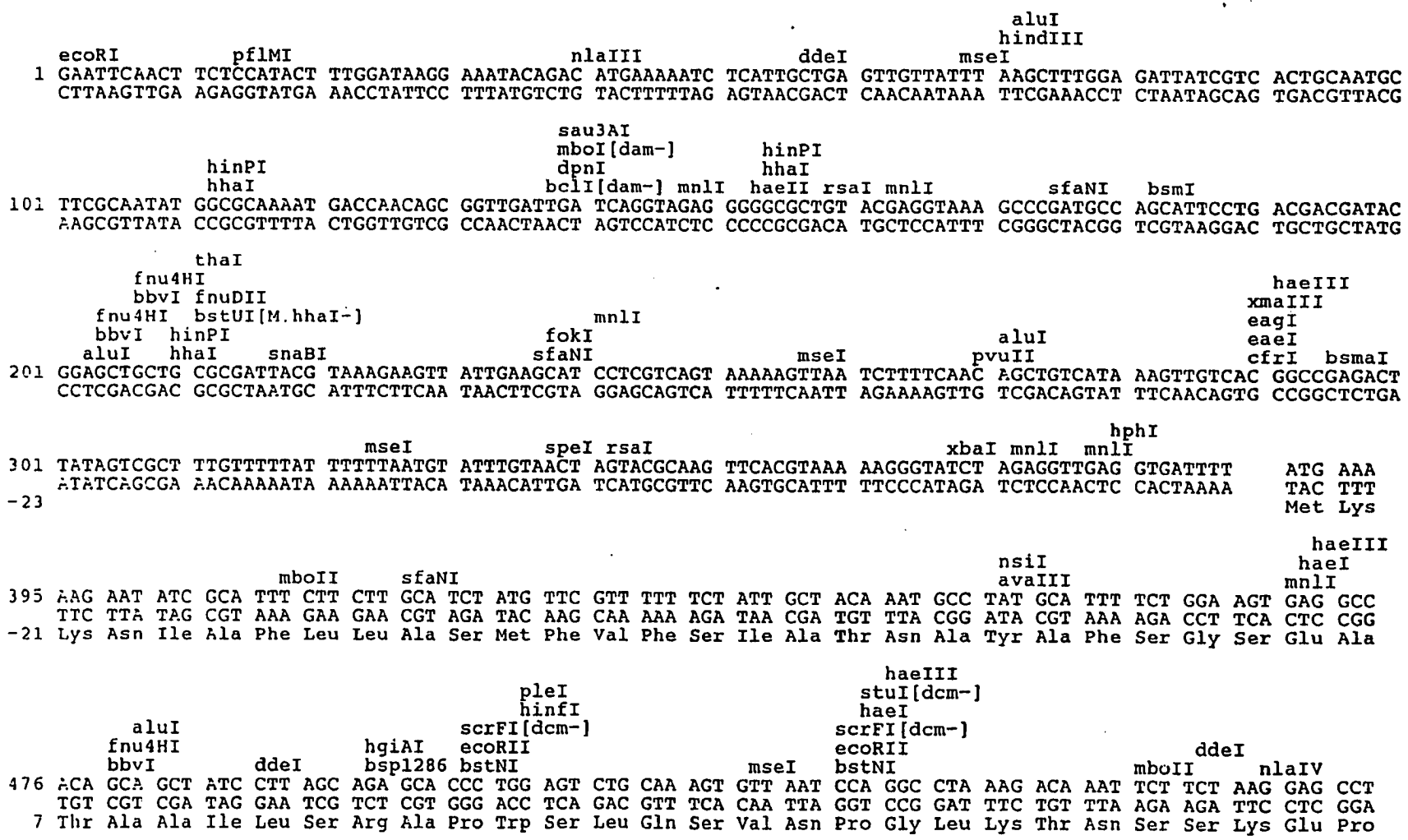


FIG.—12A

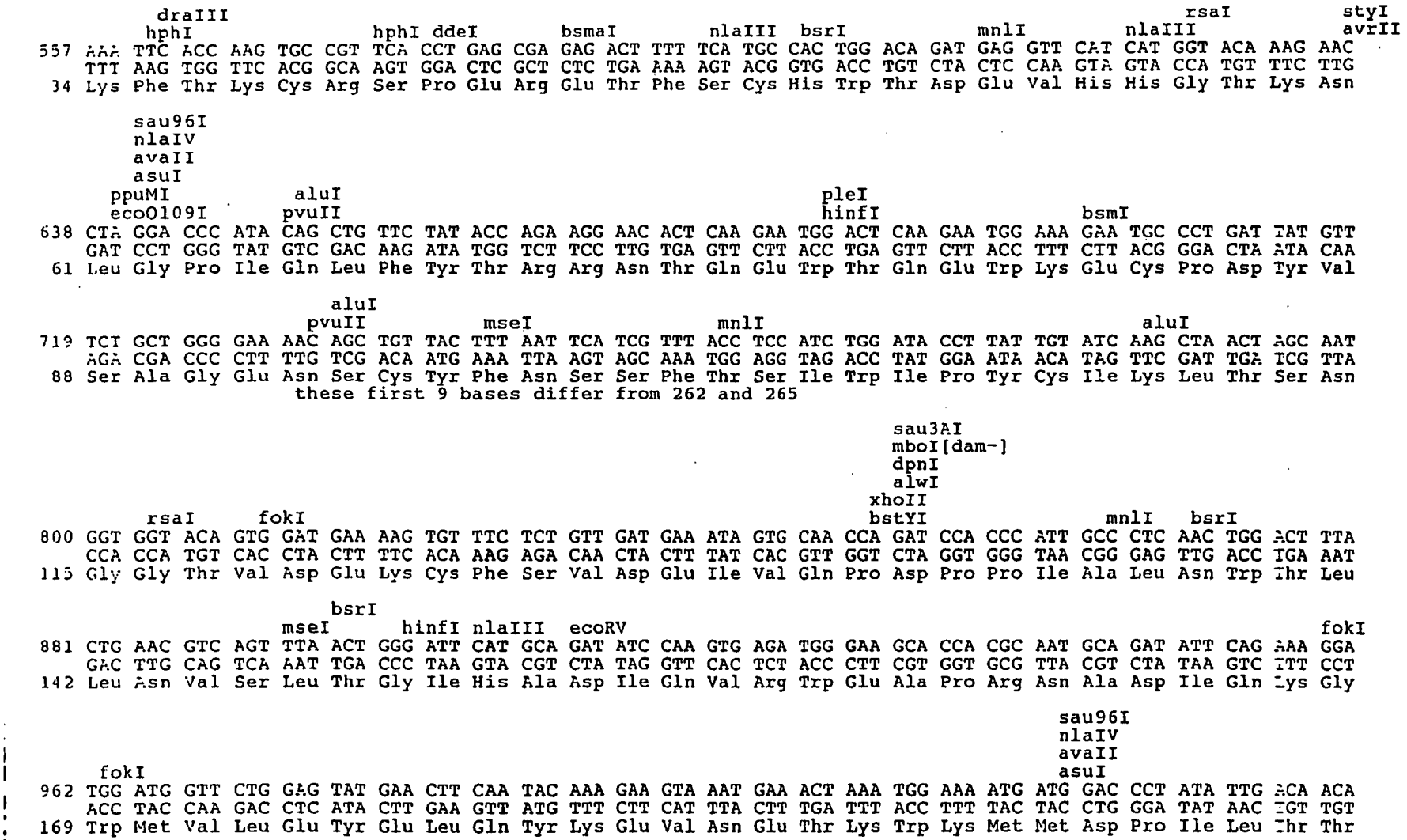

draIII
hphI
hphI ddeI
bsmaI
nlaIII bsrI
mnlI
nlaIII
rsaI
styI
avrII
557 AAA TTC ACC AAG TGC CGT TCA CCT GAG CGA GAG ACT TTT TCA TGC CAC TGG ACA GAT GAG GTT CAT CAT GGT ACA AAG AAC
TTT AAG TGG TTC ACG GCA AGT GGA CTC GCT CTC TGA AAA AGT ACG GTG ACC TGT CTA CTC CAA GTA GTA CCA TGT TTC TTG
34 Lys Phe Thr Lys Cys Arg Ser Pro Glu Arg Glu Thr Phe Ser Cys His Trp Thr Asp Glu Val His His Gly Thr Lys Asn
sau96I
nlaIV
avaII
asuI
ppuMI
eco0109I
aluI
pvuII
pleI
hinfI
bsmI
638 CTA GGA CCC ATA CAG CTG TTC TAT ACC AGA AGG AAC ACT CAA GAA TGG ACT CAA GAA TGG AAA GAA TGC CCT GAT TAT GTT
GAT CCT GGG TAT GTC GAC AAG ATA TGG TCT TCC TTG TGA GTT CTT ACC TGA GTT CTT ACC TTT CTT ACG GGA CTA ATA CAA
61 Leu Gly Pro Ile Gln Leu Phe Tyr Thr Arg Arg Asn Thr Gln Glu Trp Thr Gln Glu Trp Lys Glu Cys Pro Asp Tyr Val
aluI
pvuII
mseI
mnlI
aluI
719 TCT GCT GGG GAA AAC AGC TGT TAC TTT AAT TCA TCG TTT ACC TCC ATC TGG ATA CCT TAT TGT ATC AAG CTA ACT AGC AAT
AGA CGA CCC CTT TTG TCG ACA ATG AAA TTA AGT AGC AAA TGG AGG TAG ACC TAT GGA ATA ACA TAG TTC GAT TGA TCG TTA
88 Ser Ala Gly Glu Asn Ser Cys Tyr Phe Asn Ser Ser Phe Thr Ser Ile Trp Ile Pro Tyr Cys Ile Lys Leu Thr Ser Asn
these first 9 bases differ from 262 and 265
sau3AI
mboI[dam-]
dpnI
alwI
xhoII
bstYI
rsaI
fokI
mnlI
bsrI
800 GGT GGT ACA GTG GAT GAA AAG TGT TTC TCT GTT GAT GAA ATA GTG CAA CCA GAT CCA CCC ATT GCC CTC AAC TGG ACT TTA
CCA CCA TGT CAC CTA CTT TTC ACA AAG AGA CAA CTA CTT TAT CAC GTT GGT CTA GGT GGG TAA CGG GAG TTG ACC TGA AAT
115 Gly Gly Thr Val Asp Glu Lys Cys Phe Ser Val Asp Glu Ile Val Gln Pro Asp Pro Pro Ile Ala Leu Asn Trp Thr Leu
bsrI
mseI
hinfI nlaIII
ecoRV
fokI
881 CTG AAC GTC AGT TTA ACT GGG ATT CAT GCA GAT ATC CAA GTG AGA TGG GAA GCA CCA CGC AAT GCA GAT ATT CAG AAA GGA
GAC TTG CAG TCA AAT TGA CCC TAA GTA CGT CTA TAG GTT CAC TCT ACC CTT CGT GGT GCG TTA CGT CTA TAA GTC TTT CCT
142 Leu Asn Val Ser Leu Thr Gly Ile His Ala Asp Ile Gln Val Arg Trp Glu Ala Pro Arg Asn Ala Asp Ile Gln Lys Gly
sau96I
nlaIV
avaII
asuI
fokI
962 TGG ATG GTT CTG GAG TAT GAA CTT CAA TAC AAA GAA GTA AAT GAA ACT AAA TGG AAA ATG ATG GAC CCT ATA TTG ACA ACA
ACC TAC CAA GAC CTC ATA CTT GAA GTT ATG TTT CTT CAT TTA CTT TGA TTT ACC TTT TAC TAC CTG GGA TAT AAC TGT TGT
169 Trp Met Val Leu Glu Tyr Glu Leu Gln Tyr Lys Glu Val Asn Glu Thr Lys Trp Lys Met Met Asp Pro Ile Leu Thr Thr

FIG.—12B

27/55

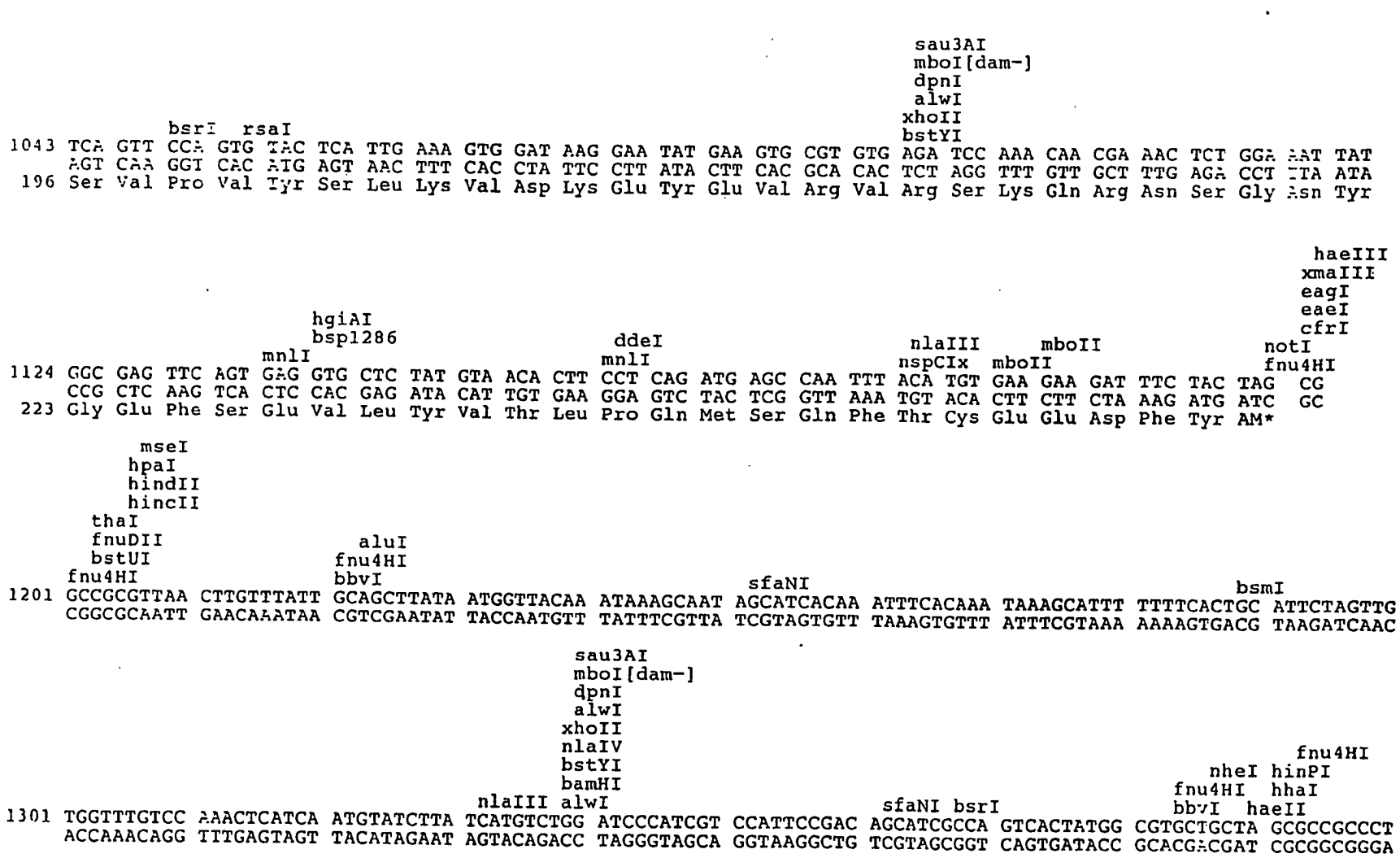

sau3AI
mboI[dam-]
dpnI
alwI
xhoII
bstYI
bsrI rsaI
1043 TCA GTT CCA GTG TAC TCA TTG AAA GTG GAT AAG GAA TAT GAA GTG CGT GTG AGA TCC AAA CAA CGA AAC TCT GGA AAT TAT
AGT CAA GGT CAC ATG AGT AAC TTT CAC CTA TTC CTT ATA CTT CAC GCA CAC TCT AGG TTT GTT GCT TTG AGA CCT TTA ATA
196 Ser Val Pro Val Tyr Ser Leu Lys Val Asp Lys Glu Tyr Glu Val Arg Val Arg Ser Lys Gln Arg Asn Ser Gly Asn Tyr
haeIII
xmaIII
eagI
eaeI
cfrI
hgiAI
bsp1286
ddeI
nlaIII mboII
mnlI
mnlI nspCIx mboII notI
fnu4HI
1124 GGC GAG TTC AGT GAG GTG CTC TAT GTA ACA CTT CCT CAG ATG AGC CAA TTT ACA TGT GAA GAA GAT TTC TAC TAG CG
CCG CTC AAG TCA CTC CAC GAG ATA CAT TGT GAA GGA GTC TAC TCG GTT AAA TGT ACA CTT CTT CTA AAG ATG ATC GC
223 Gly Glu Phe Ser Glu Val Leu Tyr Val Thr Leu Pro Gln Met Ser Gln Phe Thr Cys Glu Glu Asp Phe Tyr AM*
mseI
hpaI
hindII
hincII
thaI
fnuDII aluI
bstUI fnu4HI
fnu4HI bbvI
sfaNI
bsmI
1201 GCCGCGTTAA CTTGTTTATT GCAGCTTATA ATGGTTACAA ATAAAGCAAT AGCATCACAA ATTTCACAAA TAAAGCATTT TTTTCACTGC ATTCTAGTTG
CGGCGCAATT GAACAAATAA CGTCGAATAT TACCAATGTT TATTTCGTTA TCGTAGTGTT TAAAGTGTTT ATTTCGTAAA AAAAGTGACG TAAGATCAAC
sau3AI
mboI[dam-]
dpnI
alwI
xhoII
nlaIV
bstYI
bamHI
fnu4HI
nheI hinPI
fnu4HI hhaI
nlaIII alwI
sfaNI bsrI
bbvI haeII
1301 TGGTTTGTCC AAACTCATCA ATGTATCTTA TCATGTCTGG ATCCCATCGT CCATTCCGAC AGCATCGCCA GTCACTATGG CGTGCTGCTA GCGCCGCCCT
ACCAAACAGG TTTGAGTAGT TACATAGAAT AGTACAGACC TAGGGTAGCA GGTAAGGCTG TCGTAGCGGT CAGTGATACC GCACGACGAT CGCGGCGGGA

FIG.—12C

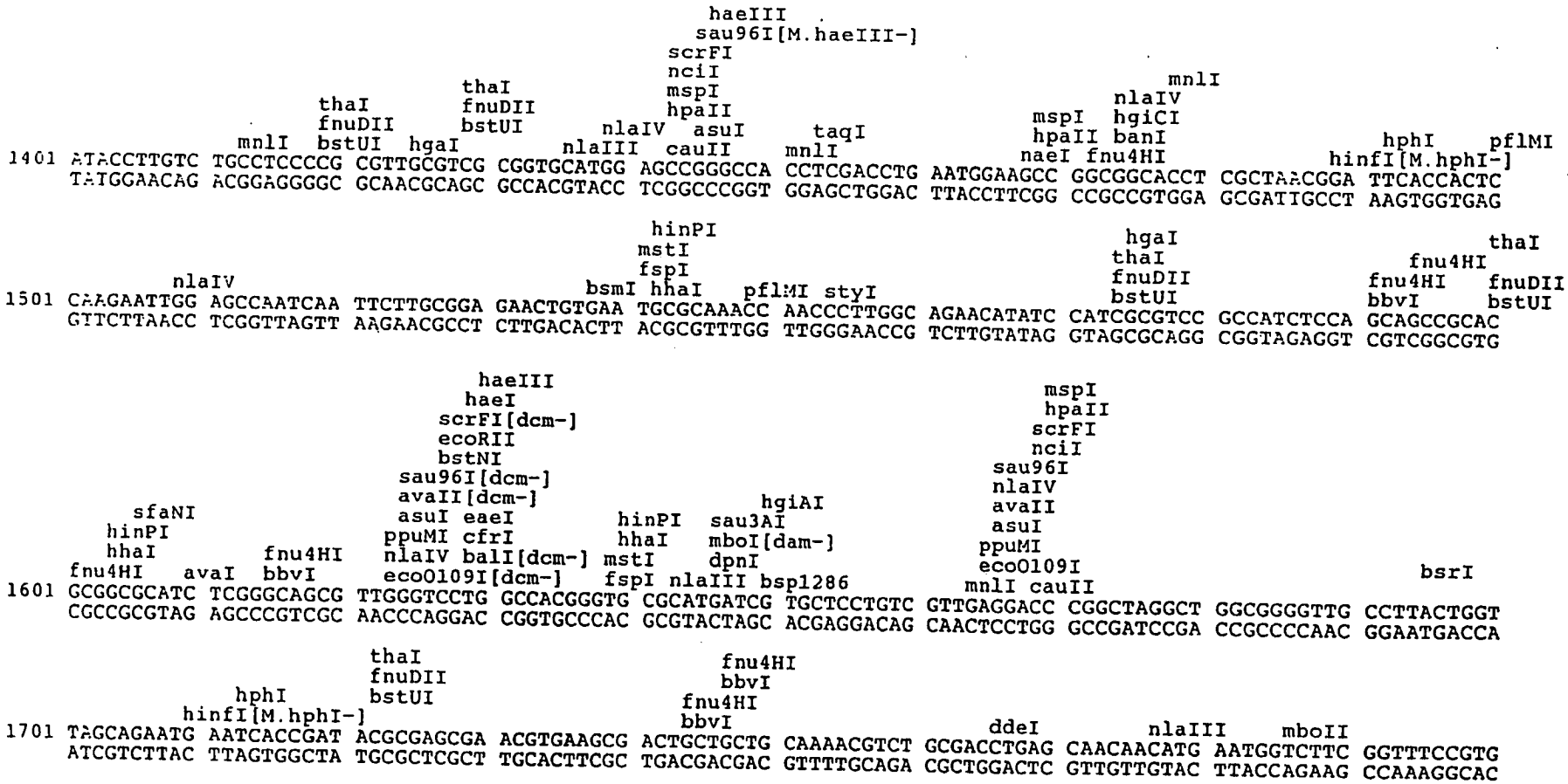

haeIII
sau96I[M.haeIII-]
scrFI
nciI
mnlI
thaI
mspI
nlaIV
fnuDII
hpaII
mspI hgiCI
mnlI bstUI hgaI
nlaIII cauII
mnlI
hpaII banI
hphI
pflMI
naeI fnu4HI
hinfI[M.hphI-]
1401 ATACCTTGTC TGCCTCCCCG CGTTGCGTCG CGGTGCATGG AGCCGGGCCA CCTCGACCTG AATGGAAGCC GGCGGCACCT CGCTAACGGA TTCACCACTC
TATGGAACAG ACGGAGGGGC GCAACGCAGC GCCACGTACC TCGGCCCGGT GGAGCTGGAC TTACCTTCGG CCGCCGTGGA GCGATTGCCT AAGTGGTGAG
hinPI
mstI
hgaI
thaI
fspI
thaI
fnu4HI
nlaIV
fnuDII
fnu4HI
fnuDII
bsmI hhaI pflMI styI
bstUI
bbvI
bstUI
1501 CAAGAATTGG AGCCAATCAA TTCTTGCGGA GAACTGTGAA TGCGCAAACC AACCCTTGGC AGAACATATC CATCGCGTCC GCCATCTCCA GCAGCCGCAC
GTTCTTAACC TCGGTTAGTT AAGAACGCCT CTTGACACTT ACGCGTTTGG TTGGGAACCG TCTTGTATAG GTAGCGCAGG CGGTAGAGGT CGTCGGCGTG
haeIII
haeI
mspI
hpaII
scrFI[dcm-]
scrFI
ecoRII
nciI
bstNI
sau96I
sau96I[dcm-]
nlaIV
avaII[dcm-]
avaII
hgiAI
sfaNI
asuI
asuI eaeI
hinPI
sau3AI
hinPI
ppuMI
ppuMI cfrI
hhaI
mboI[dam-]
hhaI
asuI
fnu4HI
nlaIV ball[dcm-]
mstI
dpnI
ppuMI
fnu4HI
avaI
bbvI
eco0109I[dcm-]
fspI nlaIII bsp1286
eco0109I
bsrI
1601 GCGGCGCATC TCGGGCAGCG TTGGGTCCTG GCCACGGGTG CGCATGATCG TGCTCCTGTC GTTGAGGACC CGGCTAGGCT GGCGGGGTTG CCTTACTGGT
CGCCGCGTAG AGCCCGTCGC AACCCAGGAC CGGTGCCCAC GCGTACTAGC ACGAGGACAG CAACTCCTGG GCCGATCCGA CCGCCCCAAC GGAATGACCA
thaI
fnu4HI
fnuDII
bbvI
hphI
bstUI
fnu4HI
hinfI[M.hphI-]
bbvI
ddeI
nlaIII
mboII
1701 TAGCAGAATG AATCACCGAT ACGCGAGCGA ACGTGAAGCG ACTGCTGCTG CAAAACGTCT GCGACCTGAG CAACAACATG AATGGTCTTC GGTTTCCGTG
ATCGTCTTAC TTAGTGGCTA TGCGCTCGCT TGCACTTCGC TGACGACGAC GTTTTGCAGA CGCTGGACTC GTTGTTGTAC TTACCAGAAG CCAAAGGCAC

FIG.—12D

```
                                                                 sau3AI
                                                                 mboI[dam-]
                                                                 dpnI
                                                                 xhoII
                                                                 bstYI
                                                                 alwI
                                                               mspI                         fnu4HI
     thaI                 hinPI                                hpaII                        bbvI
     fnuDII               hhaI                                 bspMII                   sfaNI
     bstUI              haeII                                  accIII    sfaNI         fokI
1801 TTTCGTAAAG TCTGGAAACG CGGAAGTCAG CGCCCTGCAC CATTATGTTC CGGATCTGCA TCGCAGGATG CTGCTGGCTA CCCTGTGGAA CACCTACATC
     AAAGCATTTC AGACCTTTGC GCCTTCAGTC GCGGGACGTG GTAATACAAG GCCTAGACGT AGCGTCCTAC GACGACCGAT GGGACACCTT GTGGATGTAG

                                                                                                             scrFI
                                                     sau96I                                                  nciI
                 hinPI                               nlaIV       fokI                                        mspI
                 hhaI                                avaII      sfaNI                                        hpaII
       mseI      haeII         ddeI                  asuI      fnu4HI         bsrI         mnlI        bsrI  cauII
1901 TGTATTAACG AAGCGCTGGC ATTGACCCTG AGTGATTTTT CTCTGGTCCC GCCGCATCCA TACCGCCAGT TGTTTACCCT CACAACGTTC CAGTAACCGG
     ACATAATTGC TTCGCGACCG TAACTGGGAC TCACTAAAAA GAGACCAGGG CGGCGTAGGT ATGGCGGTCA ACAAATGGGA GTGTTGCAAG GTCATTGGCC

                                          mnlI
      nlaIII                            fokI                                                                   sfaNI
     nspCIx                            sfaNI                                   nlaIII                        mnlI
2001 GCATGTTCAT CATCAGTAAC CCGTATCGTG AGCATCCTCT CTCGTTTCAT CGGTATCATT ACCCCCATGA ACAGAAATTC CCCCTTACAC GGAGGCATCA
     CGTACAAGTA GTAGTCATTG GGCATAGCAC TCGTAGGAGA GAGCAAAGTA GCCATAGTAA TGGGGGTACT TGTCTTTAAG GGGGAATGTG CCTCCGTAGT

                                         sau96I[M.haeIII-]                                                   thaI
                                         haeIII                                                              fnuDII
                                         asuI                                                                bstUI
                                   mseI nlaIII                           mseI                    aluI hgaI  fokI
2101 AGTGACCAAA CAGGAAAAAA CCGCCCTTAA CATGGCCCGC TTTATCAGAA GCCAGACATT AACGCTTCTG GAGAAACTCA ACGAGCTGGA CGCGGATGAA
     TCACTGGTTT GTCCTTTTTT GGCGGGAATT GTACCGGGCG AAATAGTCTT CGGTCTGTAA TTGCGAAGAC CTCTTTGAGT TGCTCGACCT GCGCCTACTT

                                                                    mspI[M.bamHI-]
                                                                    hpaII
                                                                   bspMII
                                                                   accIII
                                                                 sau3AI
                                                                 mboI[dam-]
                                                                 dpnI
                                                                 alwI
                                                                xhoII
                                                                nlaIV                                           mseI
                 xmnI                                           bstYI                                        thaI
                 hinfI                                          bamHI[M.mspI-]        sspI                   fnuDII
                                                   aluI         alwI               mseI          mseI        bstUI
2201 CAGGCAGACA TCTGTGAATC GCTTCACGAC CACGCTGATG AGCTTTACCG CAGGATCCGG AAATTGTAAA CGTTAATATT TTGTTAAAAT TCGCGTTAAA
     GTCCGTCTGT AGACACTTAG CGAAGTGCTG GTGCGACTAC TCGAAATGGC GTCCTAGGCC TTTAACATTT GCAATTATAA AACAATTTTA AGCGCAATTT
```

FIG.—12E

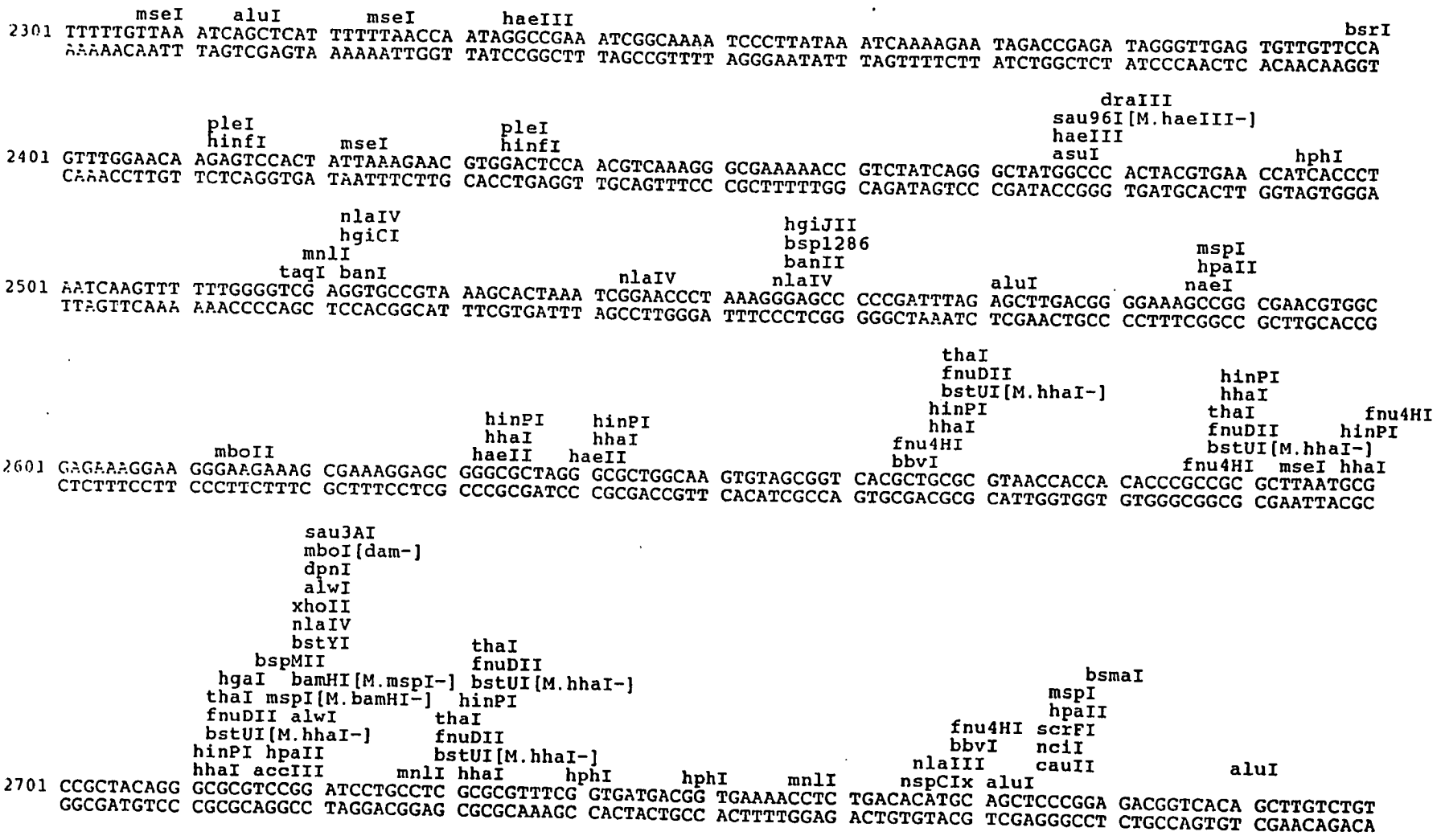


FIG.—12F

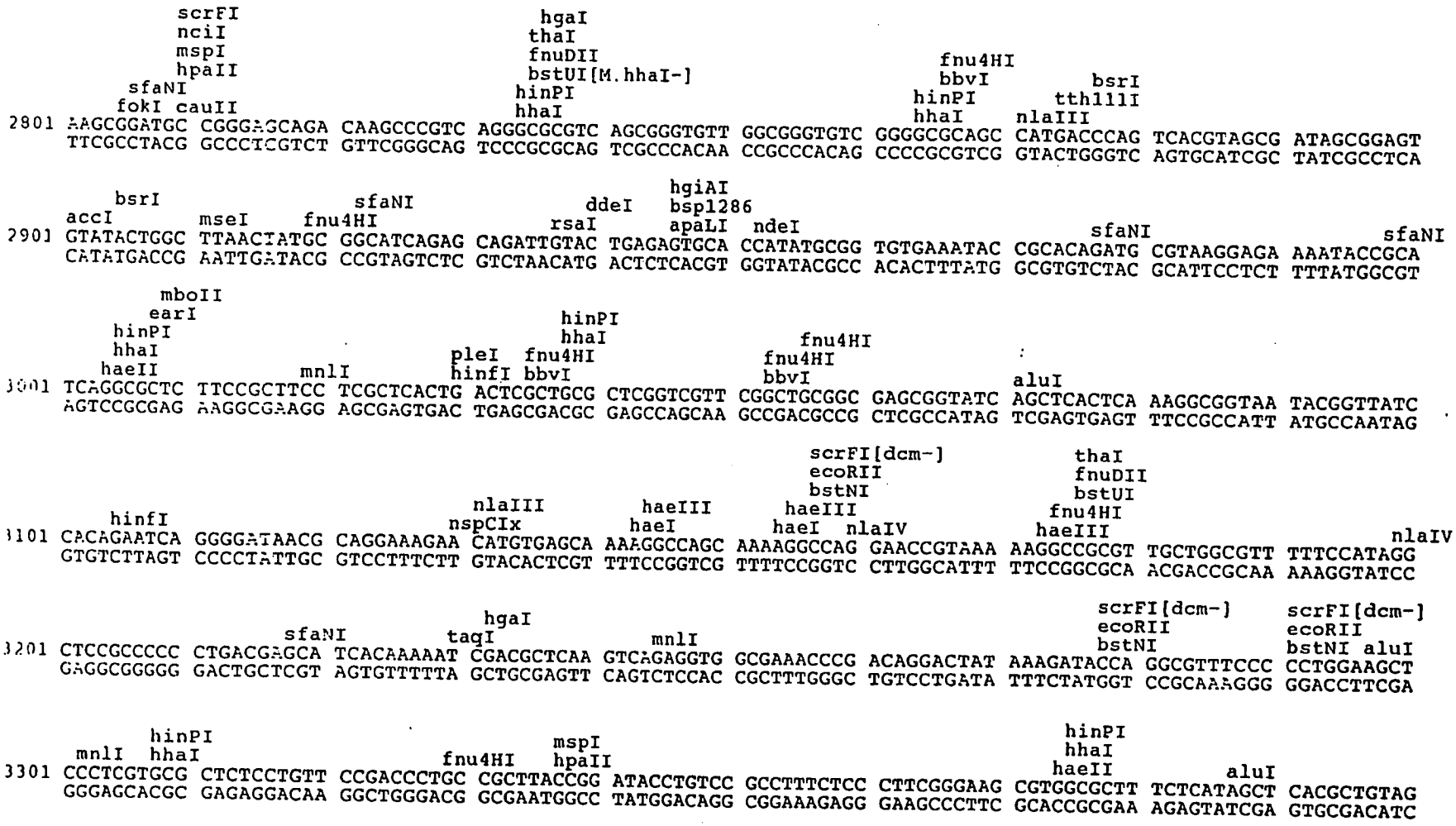


FIG.—12G

SUBSTITUTE SHEET

FIG.—12H

SUBSTITUTE SHEET

```
                                                                                bsrI
                                                                            sau96I[M.haeIII-]                bsmaI
                                                                            nlaIV                         thaI
       fokI            pleI                                                 haeIII     fnu4HI             fnuDII
                       hinfI                                   mnlI         asuI       bbvI               bstUI
4001 TTCATCCATA GTTGCCTGAC TCCCCGTCGT GTAGATAACT ACGATACGGG AGGGCTTACC ATCTGGCCCC AGTGCTGCAA TGATACCGCG AGACCCACGC
     AAGTAGGTAT CAACGGACTG AGGGGCAGCA CATCTATTGA TGCTATGCCC TCCCGAATGG TAGACCGGGG TCACGACGTT ACTATGGCGC TCTGGGTGCG

                                                        haeIII
        mspI                                 mspI     sau96I[M.haeIII-]  sau96I
        hpaII                                hpaII    asuI       hinPI   avaII                        bsrI     mseI
     hphI nlaIV                             bglI[M.haeIII-]     hhaI    asuI                 mnlI fokI        aseI
4101 TCACCGGCTC CAGATTTATC AGCAATAAAC CAGCCAGCCG GAAGGGCCGA GCGCAGAAGT GGTCCTGCAA CTTTATCCGC CTCCATCCAG TCTATTAATT
     AGTGGCCGAG GTCTAAATAG TCGTTATTTG GTCGGTCGGC CTTCCCGGCT CGCGTCTTCA CCAGGACGTT GAAATAGGCG GAGGTAGGTC AGATAATTAA

      scrFI
      nciI                                          hinPI
      mspI                                          hhaI
      hpaII                                        mstI               pstI[M.H1-]
      cauII  aluI                  bsrI mseI       fspI               fnu4HI
                                                                     bbvI    sfaNI
4201 GTTGCCGGGA AGCTAGAGTA AGTAGTTCGC CAGTTAATAG TTTGCGCAAC GTTGTTGCCA TTGCTGCAGG CATCGTGGTG TCACGCTCGT CGTTTGGTAT
     CAACGGCCCT TCGATCTCAT TCATCAAGCG GTCAATTATC AAACGCGTTG CAACAACGGT AACGACGTCC GTAGCACCAC AGTGCGAGCA GCAAACCATA

                                                    sau3AI
                                                    mboI[dam-]
                 mspI        sau3AI                 dpnI                                        mnlI  sau3AI
                 hpaII       mboI[dam-]             alwI                                    sau96I   mboI[dam-]
                                                                                            avaII    dpnI
            aluI  nlaIV      dpnI                 nlaIII    nlaIII                 aluI     asuI   pvuI
4301 GGCTTCATTC AGCTCCGGTT CCCAACGATC AAGGCGAGTT ACATGATCCC CCATGTTGTG CAAAAAAGCG GTTAGCTCCT TCGGTCCTCC GATCGTTGTC
     CCGAAGTAAG TCGAGGCCAA GGGTTGCTAG TTCCGCTCAA TGTACTAGGG GGTACAACAC GTTTTTTCGC CAATCGAGGA AGCCAGGAGG CTAGCAACAG

              fnu4HI
             haeIII
            eaeI                              fnu4HI                                  fokI                      hphI
            cfrI                   nlaIII    bbvI                             nlaIII        sfaNI           bsrI
4401 AGAAGTAAGT TGGCCGCAGT GTTATCACTC ATGGTTATGG CAGCACTGCA TAATTCTCTT ACTGTCATGC CATCCGTAAG ATGCTTTTCT GTGACTGGTG
     TCTTCATTCA ACCGGCGTCA CAATAGTGAG TACCAATACC GTCGTGACGT ATTAAGAGAA TGACAGTACG GTAGGCATTC TACGAAAAGA CACTGACCAC

                                                                    hgaI
                                                                   ahaII[M.hpaII-]
                                                                   acyI
                                                                 mspI                        hinPI
                                                                 hpaII                       hhaI
       rsaI                                                     scrFI                      thaI                mseI
      scaI                ddeI              fnu4HI              nciI     hindII            fnuDII              draI
                                                                cauII    hincII            bstUI[M.hhaI-]     ahaIII
4501 AGTACTCAAC CAAGTCATTC TGAGAATAGT GTATGCGGCG ACCGAGTTGC TCTTGCCCGG CGTCAACACG GGATAATACC GCGCCACATA GCAGAACTTT
     TCATGAGTTG GTTCAGTAAG ACTCTTATCA CATACGCCGC TGGCTCAACG AGAACGGGCC GCAGTTGTGC CCTATTATGG CGCGGTGTAT CGTCTTGAAA
```

FIG.—12I

```
                                                                                                        bsrI
                                                                                   sau3AI              sau3AI
                                                                                   mboI[dam-]          mboI[dam-]
                                                                                   dpnI                dpnI
                                                                                  xhoII                alwI
      hgiAI                                                                       bstYI               xhoII                            hgiAI
      bsp1286          xmnI        mboII                                          alwI                bstYI      taqI                 bsp1286
4601 AAAAGTGCTC ATCATTGGAA AACGTTCTTC GGGGCGAAAA CTCTCAAGGA TCTTACCGCT GTTGAGATCC AGTTCGATGT AACCCACTCG TGCACCCAAC
     TTTTCACGAG TAGTAACCTT TTGCAAGAAG CCCCGCTTTT GAGAGTTCCT AGAATGGCGA CAACTCTAGG TCAAGCTACA TTGGGTGAGC ACGTGGGTTG

      mboII[dam-]
    sau3AI
    mboI[dam-]
    dpnI    sfaNI          hphI               hphI                                  fnu4HI
4701 TGATCTTCAG CATCTTTTAC TTTCACCAGC GTTTCTGGGT GAGCAAAAAC AGGAAGGCAA AATGCCGCAA AAAAGGGAAT AAGGGCGACA CGGAAATGTT
     ACTAGAAGTC GTAGAAAATG AAAGTGGTCG CAAAGACCCA CTCGTTTTTG TCCTTCCGTT TTACGGCGTT TTTTCCCTTA TTCCCGCTGT GCCTTTACAA

                                                                             nlaIII
             mboII                                                          bspHI
             earI            sspI                                         bsmaI
4801 GAATACTCAT ACTCTTCCTT TTTCAATATT ATTGAAGCAT TTATCAGGGT TATTGTCTCA TGAGCGGATA CATATTTGAA TGTATTTAGA AAAATAAACA
     CTTATGAGTA TGAGAAGGAA AAAGTTATAA TAACTTCGTA AATAGTCCCA ATAACAGAGT ACTCGCCTAT GTATAAACTT ACATAAATCT TTTTATTTGT

             hinPI                                                                                                 sau96I
             hhaI                                                                                                  haeIII
             thaI                                  ahaII                                                           asuI
             fnuDII                                acyI ddeI                 nlaIII                                 eco0109I
        nlaIV bstUI[M.hhaI-]                       aatII                    bspHI       mseI                       mnlI
4901 AATAGGGGTT CCGCGCACAT TTCCCCGAAA AGTGCCACCT GACGTCTAAG AAACCATTAT TATCATGACA TTAACCTATA AAAATAGGCG TATCACGAGG
     TTATCCCCAA GGCGCGTGTA AAGGGGCTTT TCACGGTGGA CTGCAGATTC TTTGGTAATA ATAGTACTGT AATTGGATAT TTTTATCCGC ATAGTGCTCC

          mboII
5001 CCCTTTCGTC TTCAA
     GGGAAAGCAG AAGTT

>length: 5015

aatII(GACGTC):        4941
accI(GTMKAC):         2901
accIII(TCCGGA):       1849 2256 2716
acyI(GRCGYC):         4559 4941
ahaII(GRCGYC):        4559[M.hpaII-] 4941
ahaIII(TTTAAA):       3887 3906 4598
aluI(AGCT):           72 203 271 481 651 734 786 1223 2184 2241 2314 2571 2771 2790 3071 3297 3387
                      3433 3690 4211 4311 4374
```

FIG.—12J

```
alwI(GGATC):            851 1095 1339 1340 1852 2253 2254 2719 2720 3697 3771 3783 3868 3881 4345 4648
                        4666
alwNI(CAGNNNCTG):       3541
apaLI(GTGCAC):          2946 3444 4690
aseI(ATTAAT):           4194
asuI(GGNCC):            641 1024 1445 1624 1666 1945 2134 2476 4065 4144 4161 4383 4999
avaI(CYCGRG):           1610
avaII(GGWCC):           641 1024 1624[dcm-] 1666 1945 4161 4383
avaIII(ATGCAT):         453
avrII(CCTAGG):          637
ball(TGGCCA):           1629[dcm-]
bamHI(GGATCC):          1339 2253[M.mspI-] 2719[M.mspI-]
banI(GGYRCC):           1474 2522 3971
banII(GRGCYC):          2556
bbvI(GCAGC):            204 207 479 1221 1384 1591 1615 1744 1747 1870 2664 2769 2866 3035 3053 3472
                        3537 3540 3746 4074 4263 4440
bclI[dam-](TGATCA):     138
bglI(GCCNNNNNGGC):      4137[M.haeIII-]
bsmI(GAATGC):           182 701 1289 1538
bsmaI(GTCTC):           295 587 2779 4090 4855
bsp1286(GDGCHC):        495 1139 1650 2556 2946 3444 4605 4690
bspHI(TCATGA):          3850 4858 4963
bspMII(TCCGGA):         1849 2256 2716
bsrI(ACTGG):            603 870 896 1049 1368 1695 1966 1990 2398 2877 2905 3533 3546 3663 4069 4187
                        4230 4494 4669
bstNI(CCWGG):           501 524 1627 3157 3278 3291
bstUI(CGCG):            211[M.hhaI-] 1203 1419 1429 1574 1600 1722 1819 2191 2292 2668[M.hhaI-] 2688[M.hhaI-]
                        2712[M.hhaI-] 2730[M.hhaI-] 2732[M.hhaI-] 2835[M.hhaI-] 3176 3757[M.hhaI-] 4087
                        4580[M.hhaI-] 4912[M.hhaI-]
bstYI(RGATCY):          850 1094 1339 1852 2253 2719 3771 3782 3868 3880 4648 4665
cauII(CCSGG):           1443 1669 1997 2775 2810 3509 4205 4556
cfrI(YGGCCR):           290 1199 1629 4411
ddeI(CTNAG):            57 488 546 579 1158 1766 1928 2940 3405 3814 3980 4520 4946
dpnI(GATC):             139 851 1095 1340 1646 1853 2254 2720 3697 3772 3783 3791 3869 3881 3986 4327
                        4345 4391 4649 4666 4702
draI(TTTAAA):           3887 3906 4598
draIII(CACNNNGTG):      562 2480
eaeI(YGGCCR):           290 1199 1629 4411
eagI(CGGCCG):           290 1199
earI(CTCTTC):           3008 4812
eco0109I(RGGNCCY):      640 1623[dcm-] 1665 4998
ecoRI(GAATTC):          1
ecoRII(CCWGG):          501 524 1627 3157 3278 3291
ecoRV(GATATC):          911
```

FIG.—12K

fnuHI(GCNGC): 204 207 479 1198 1201 1221 1384 1393 1472 1591 1594 1601 1615 1744 1747 1870 1951 2664 2686 2700 2769 2866 2919 3035 3053 3056 3174 3329 3472 3537 3540 3746 4074 4263 4413 4440 4535 4764

fnuDII(CGCG): 211 1203 1419 1429 1574 1600 1722 1819 2191 2292 2668 2688 2712 2730 2732 2835 3176 3757 4087 4580 4912

fokI(GGATG): 238 811 959 963 1866 1955 2033 2194 2805 4003 4184 4471

fspI(TGCGCA): 1541 1639 4243

haeI(WGGCCW): 471 526 1629 3143 3154 3606

haeII(RGCGCY): 153 1390 1829 1912 2632 2640 3004 3374

haeIII(GGCC): 291 472 527 1200 1446 1630 2134 2334 2476 3144 3155 3173 3607 4065 4145 4412 4999

hgaI(GACGC): 1425 1575 2189 2713 2836 3232 3810 4560

hgiAI(GWGCWC): 495 1139 1650 2946 3444 4605 4690

hgiCI(GGYRCC): 1474 2522 3971

hgiJII(GRGCYC): 2556

hhaI(GCGC): 112 154 210 1391 1542 1604 1640 1830 1913 2633 2641 2667 2689 2698 2711 2731 2834 2864 3005 3038 3308 3375 3475 3649 3758 4151 4244 4581 4913

hinPI(GCGC): 112 154 210 1391 1542 1604 1640 1830 1913 2633 2641 2667 2689 2698 2711 2731 2834 2864 3005 3038 3308 3375 3475 3649 3758 4151 4244 4581 4913

hincII(GTYRAC): 1206 4562

hindII(GTYRAC): 1206 4562

hindIII(AAGCTT): 71

hinfI(GANTC): 505 685 901 1489[M.hphI-] 1710[M.hphI-] 2216 2412 2434 3030 3105 3501 4018

hpaI(GTTAAC): 1206

hpaII(CCGG): 1443 1469 1670 1850 1997 2257 2587 2717 2776 2810 3337 3484 3510 3700 4104 4138 4205 4315 4557

hphI(GGTGA): 380 561 575 1492 1713 2494 2740 2749 3874 4101 4497 4723 4738

mboII(GAAGA): 409 542 1181 1184 1786 2613 3009 3780[dam-] 3871[dam-] 4626 4704[dam-] 4813 5009

mboI[dam-](GATC): 139 851 1095 1340 1646 1853 2254 2720 3697 3772 3783 3791 3869 3881 3986 4327 4345 4391 4649 4666 4702

mnlI(CCTC): 148 163 241 372 378 470 614 759 865 1136 1157 1413 1451 1478 1664 1978 2036 2092 2520 2727 2757 3019 3245 3302 3569 3969 4050 4180 4386 4997

mseI(TTAA): 69 257 324 519 744 893 1207 1905 2127 2159 2273 2284 2296 2307 2324 2422 2693 2911 3836 3888 3893 3907 3960 4195 4234 4599 4971

mspI(CCGG): 1443 1469 1670 1850 1997 2257[M.bamHI-] 2587 2717[M.bamHI-] 2776 2810 3337 3484 3510 3700 4104 4138 4205 4315 4557

mstI(TGCGCA): 1541 1639 4243

naeI(GCCGGC): 1468 2586

nciI(CCSGG): 1443 1669 1997 2775 2810 3509 4205 4556

ndeI(CATATG): 2952

nheI(GCTAGC): 1387

FIG.—12L

```
nlaIII(CATG):           40 597 623 905 1176 1332 1436 1643 1777 2002 2066 2131 2766 2871 3131 3851 4342
                        4352 4430 4466 4859 4964
nlaIV(GGNNCC):          550 641 1024 1339 1439 1474 1509 1623 1666 1945 2253 2522 2543 2555 2719 3160
                        3199 3971 4065 4106 4317 4907
notI(GCGGCCGC):         1198
nsiI(ATGCAT):           453
nspCIx(RCATGY):         1175 2001 2765 3130
pflMI(CCANNNNNTGG):     14 1500 1549
pleI(GAGTC):            505 685 2412 2434 3030 3501 4018
ppuMI(RGGWCCY):         640 1623 1665
pstI(CTGCAG):           4264[M.H1-]
pvuI(CGATCG):           4390
pvuII(CAGCTG):          270 650 733
rsaI(GTAC):             159 342 627 804 1054 2937 4502
sau3AI(GATC):           139 851 1095 1340 1646 1853 2254 2720 3697 3772 3783 3791 3869 3881 3986 4327
                        4345 4391 4649 4666 4702
sau96I(GGNCC):          641 1024 1445[M.haeIII-] 1624[dcm-] 1666 1945 2134[M.haeIII-] 2476[M.haeIII-]
                        4065[M.haeIII-] 4144[M.haeIII-] 4161 4383 4999[M.haeIII-]
scaI(AGTACT):           4501
scrFI(CCSGG):           1443 1669 1997 2775 2810 3509 4205 4556
scrFI[dcm-](CCWGG):     501 524 1627 3157 3278 3291
sfaNI(GCATC):           175 237 416 1252 1362 1606 1858 1867 1954 2032 2095 2806 2922 2977 2998 3218
                        4270 4480 4710
snaBI(TACGTA):          217
speI(ACTAGT):           338
sspI(AATATT):           2275 4825
stuI(AGGCCT):           526[dcm-]
styI(CCWWGG):           637 1554
taqI(TCGA):             1453 2518 3230 4674
thaI(CGCG):             211 1203 1419 1429 1574 1600 1722 1819 2191 2292 2668 2688 2712 2730 2732 2835
                        3176 3757 4087 4580 4912
tth111I(GACNNNGTC):     2874
xbaI(TCTAGA):           368
xhoII(RGATCY):          850 1094 1339 1852 2253 2719 3771 3782 3868 3880 4648 4665
xmaIII(CGGCCG):         290 1199
xmnI(GAANNNNTTC):       2216 4618
not found:
```

aflII(CTTAAG), apaI(GGGCCC), asp718(GGTACC), asuII(TTCGAA), bglII(AGATCT), bspMI(ACCTGC), bssHII(GCGCGC), bstBI(TTCGAA), bstEII(GGTNACC), bstXI(CCANNNNNNTGG), bsu36I(CCTNAGG), claI(ATCGAT), eco81I(CCTNAGG), ecoNI(CCTNNNNNAGG), espI(GCTNAGC), kpnI(GGTACC), mluI(ACGCGT), mstII(CCTNAGG), narI(GGCGCC), ncoI(CCATGG), nruI(TCGCGA), paeR7I(CTCGAG), rsrII(CGGWCCG), sacI(GAGCTC), sacII(CCGCGG), salI(GTCGAC), sfiI(GGCCNNNNNGGCC), smaI(CCCGGG), sphI(GCATGC), sstI(GAGCTC), xhoI(CTCGAG), xmaI(CCCGGG)

FIG.—12M

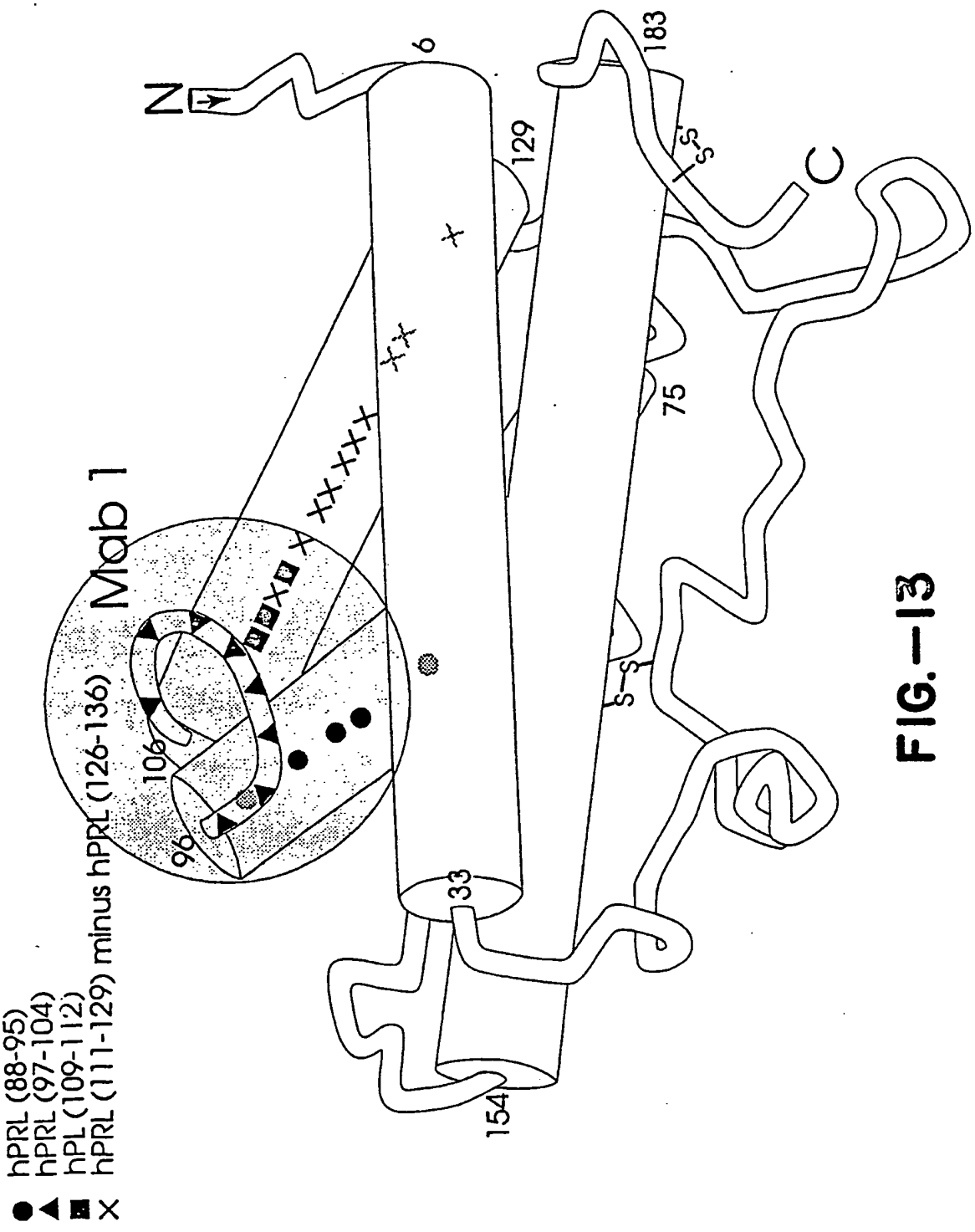

N
C
6
129
183
75
33
154
96
106
Mab 1
hPRL (126-136)
hPRL (88-95)
hPRL (97-104)
hPL (109-112)
hPRL (111-129) minus hPRL (126-136)

FIG.—13

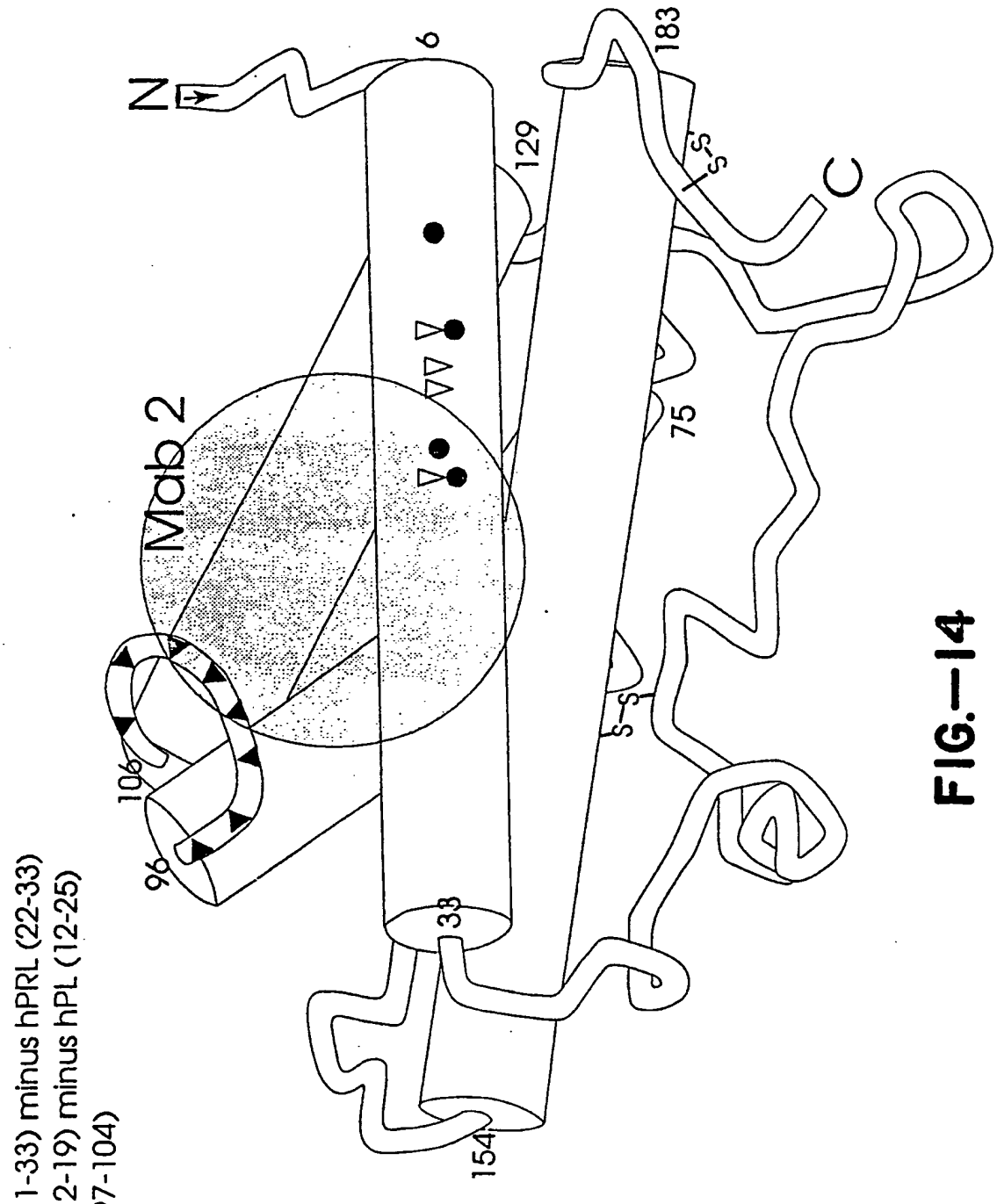

N
6
129
183
S-S
C
Mab 2
75
S-S
S-S
106
96
38
154
● pGH (11-33) minus hPRL (22-33)
▽ hPRL (12-19) minus hPL (12-25)
▲ hPRL (97-104)

FIG.—14

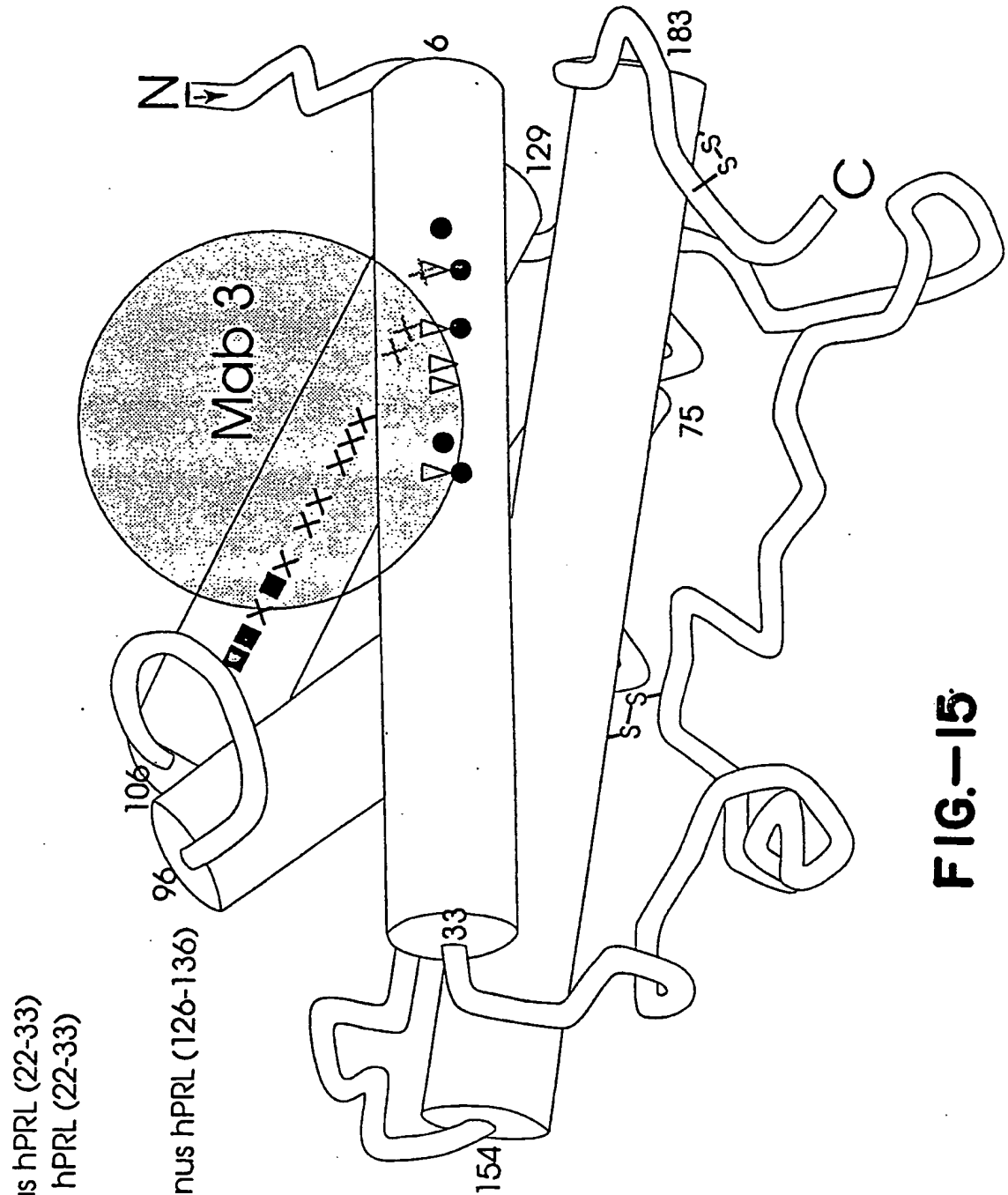

N
C
Mab 3
6
129
183
75
106
96
33
154
S-S
S-S
S-S
● pGH (11-33) minus hPRL (22-33)
▲ hPL (12-25) minus hPRL (22-33)
▽ hPRL (12-79)
■ hPL (109-112)
× hPRL (111-129) minus hPRL (126-136)

FIG.—15

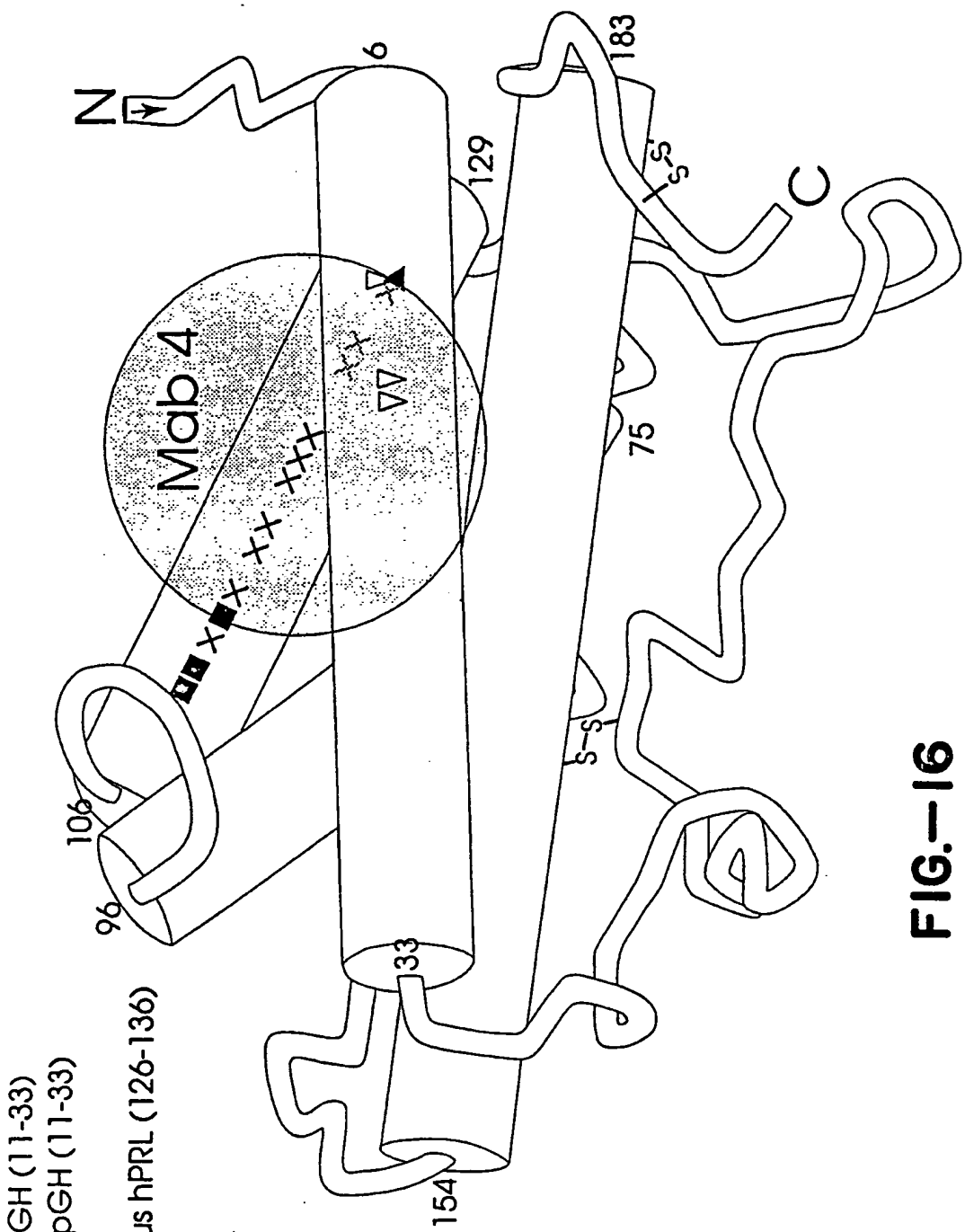

N
6
129
183
S-S
C
Mab 4
75
S-S
106
96
33
154
▲ hPL (12-25) minus pGH (11-33)
▽ hPRL (12-19) minus pGH (11-33)
■ hPL (109-112)
× hPRL (111-129) minus hPRL (126-136)

FIG.—16

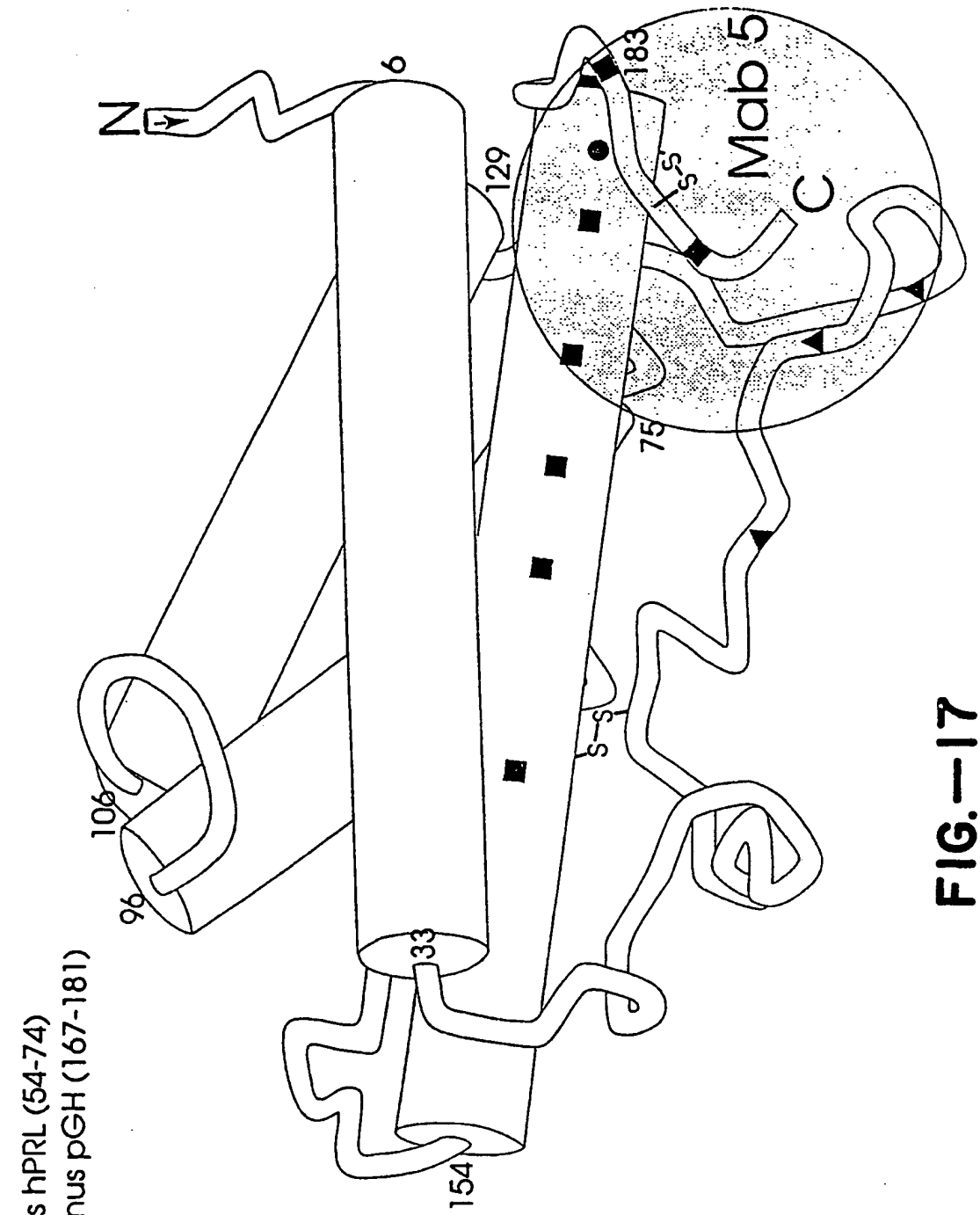

N
6
129
183
S-S
Mab 5
C
75
S-S
106
96
33
154
▲ ■ ●
pGH (57-73) minus hPRL (54-74)
pGH (164-190) minus pGH (167-181)
C182A

FIG.—17

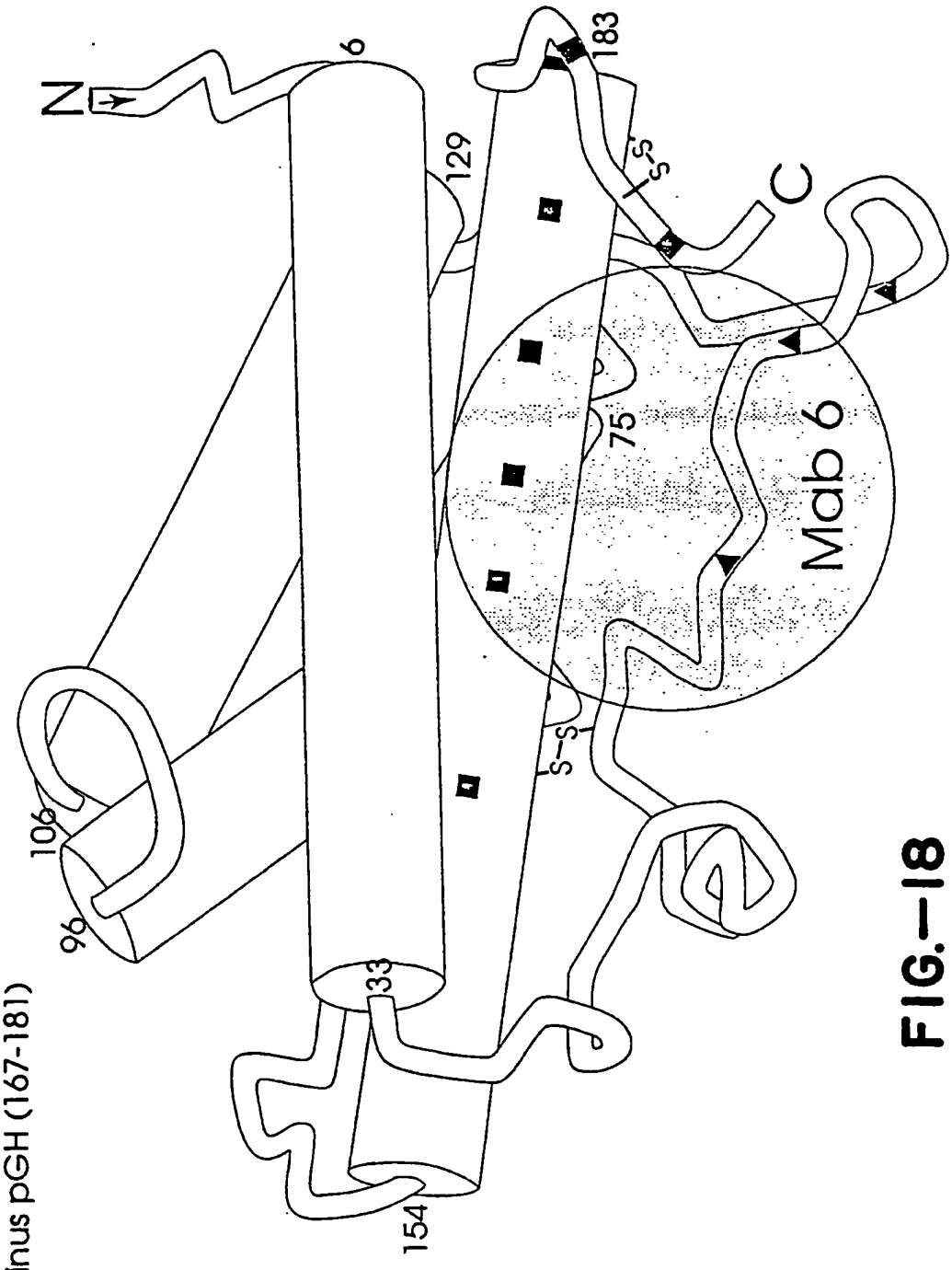

N
6
129
183
S-S
C
75
Mab 6
S-S
106
96
33
154
▲ ■ pGH (57-73) minus hPRL (54-74)
pGH (164-190) minus pGH (167-181)

FIG.—18

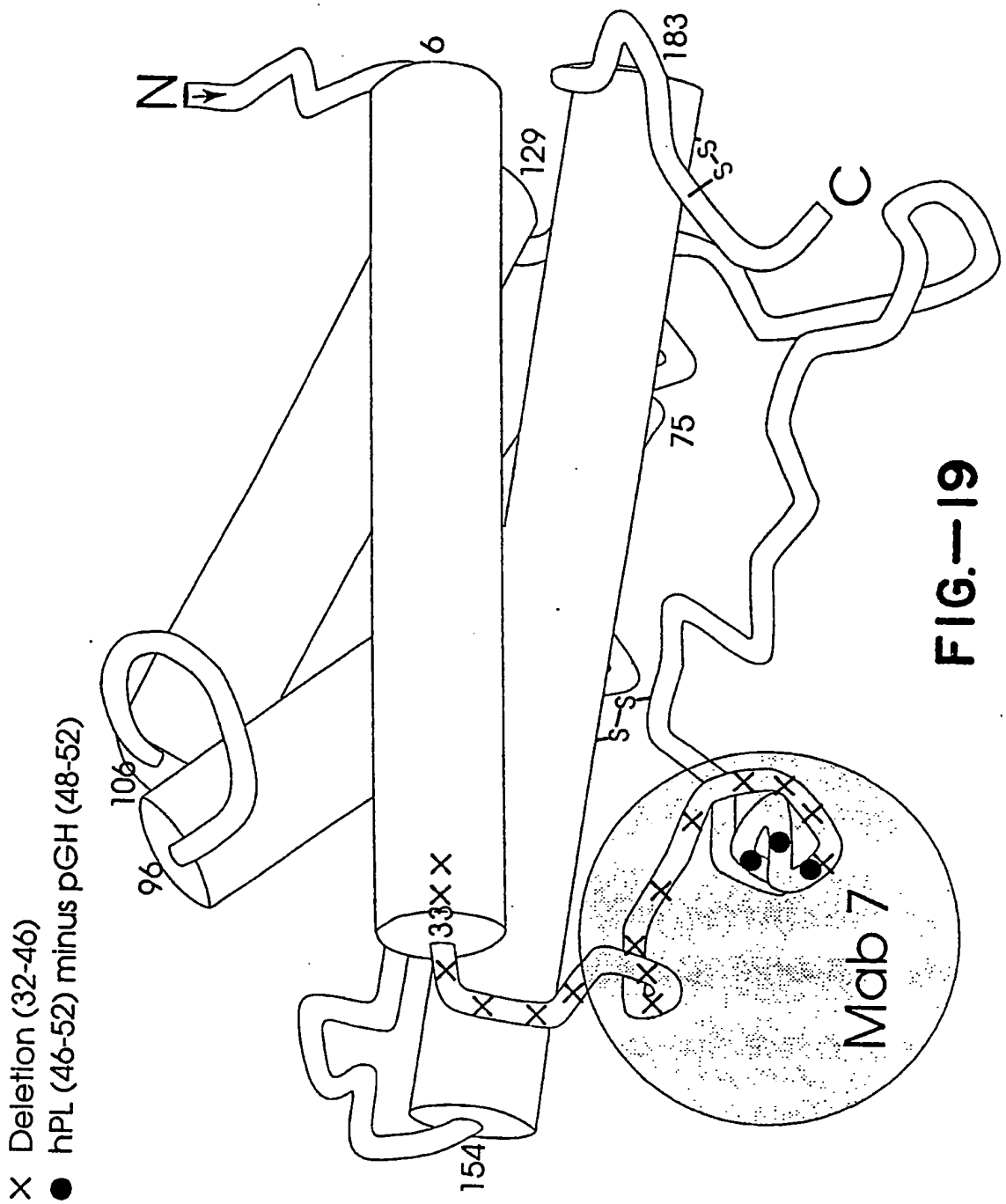

N
C
6
129
183
S-S
S-S
S-S
75
106
96
33
154
Mab 7
X Deletion (32-46)
● hPL (46-52) minus pGH (48-52)

FIG.—19

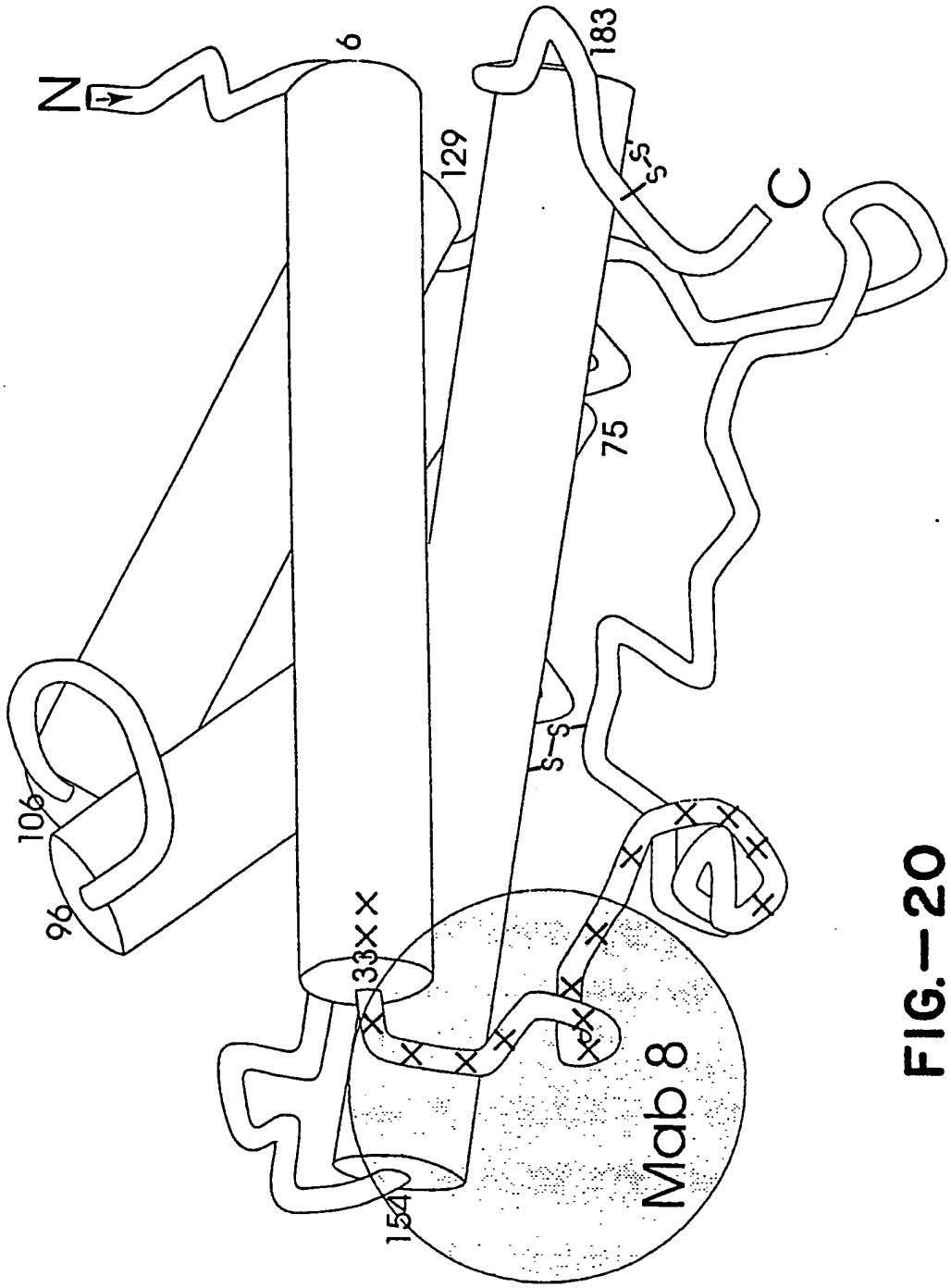


FIG.—20

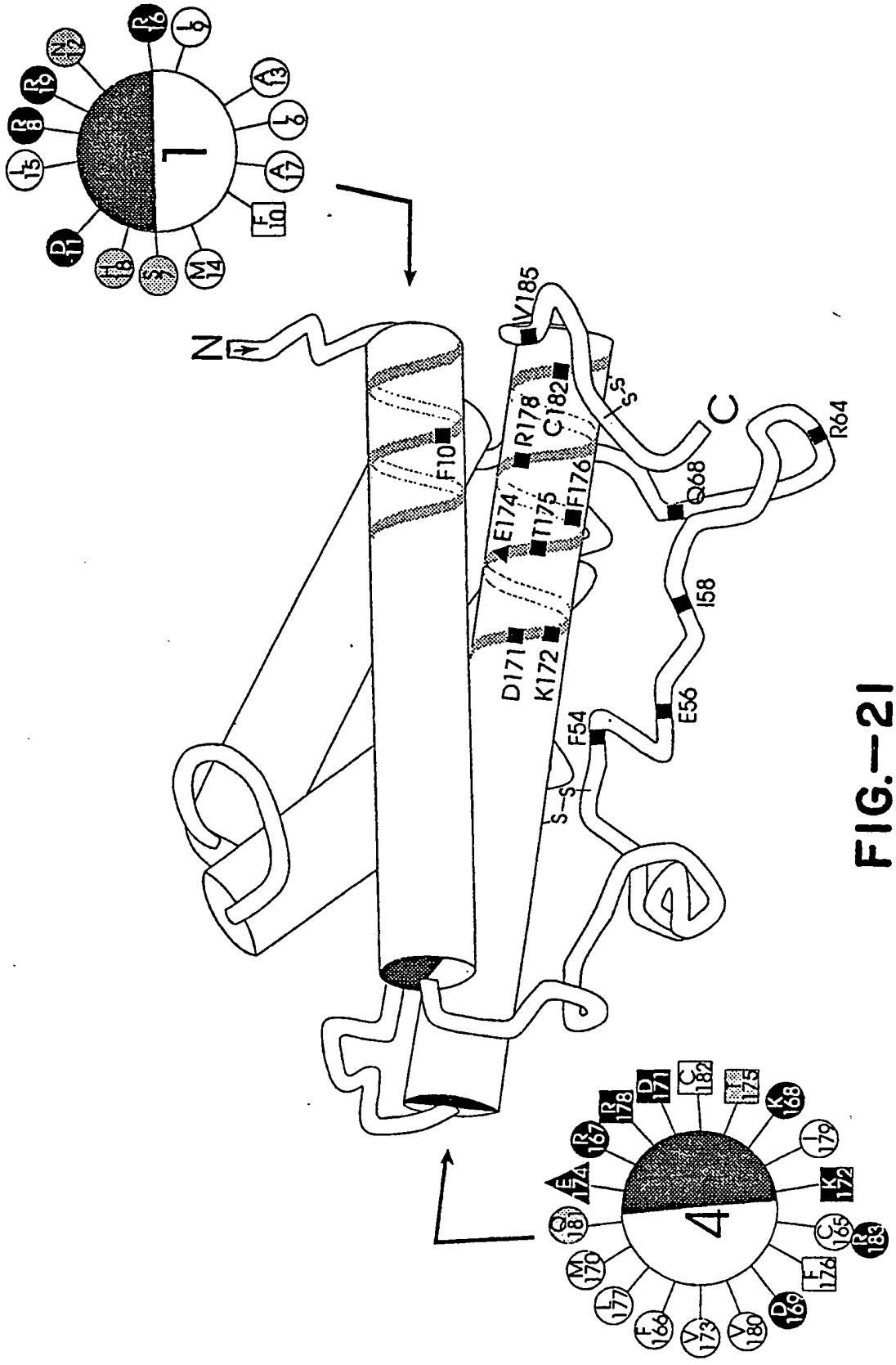

N
C
V185
C182
R178
S-S
R64
F10
Q68
F176
E174
T175
158
D171
K172
E56
F54
S-S
1
4

FIG.—21

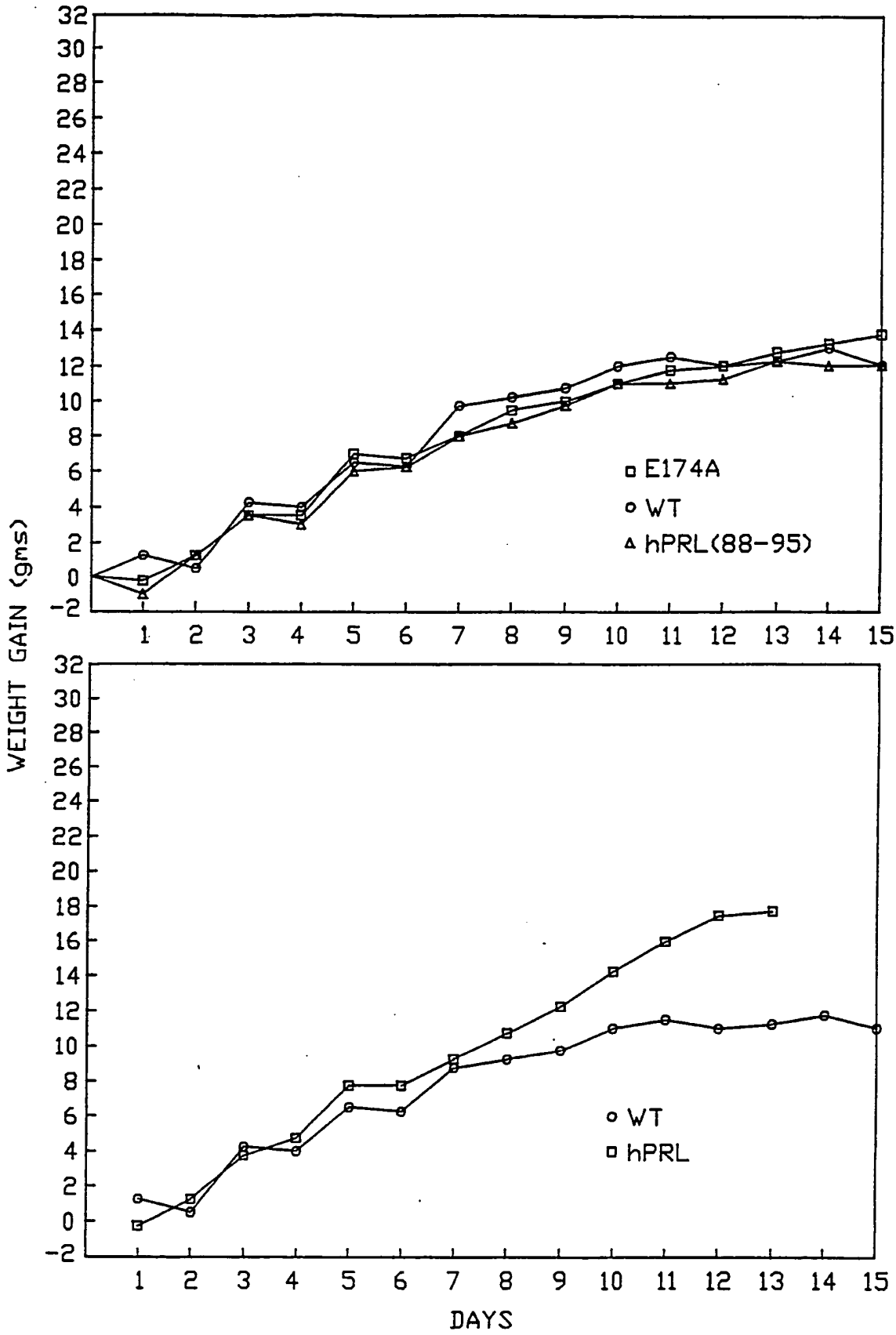

WEIGHT GAIN (gms)
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
-2
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
E174A
WT
hPRL(88-95)
WT
hPRL
DAYS

FIG.—22

GH ANALOG BIOPOTENCY IN RATS AFTER 8 DAYS OF TREATMENT

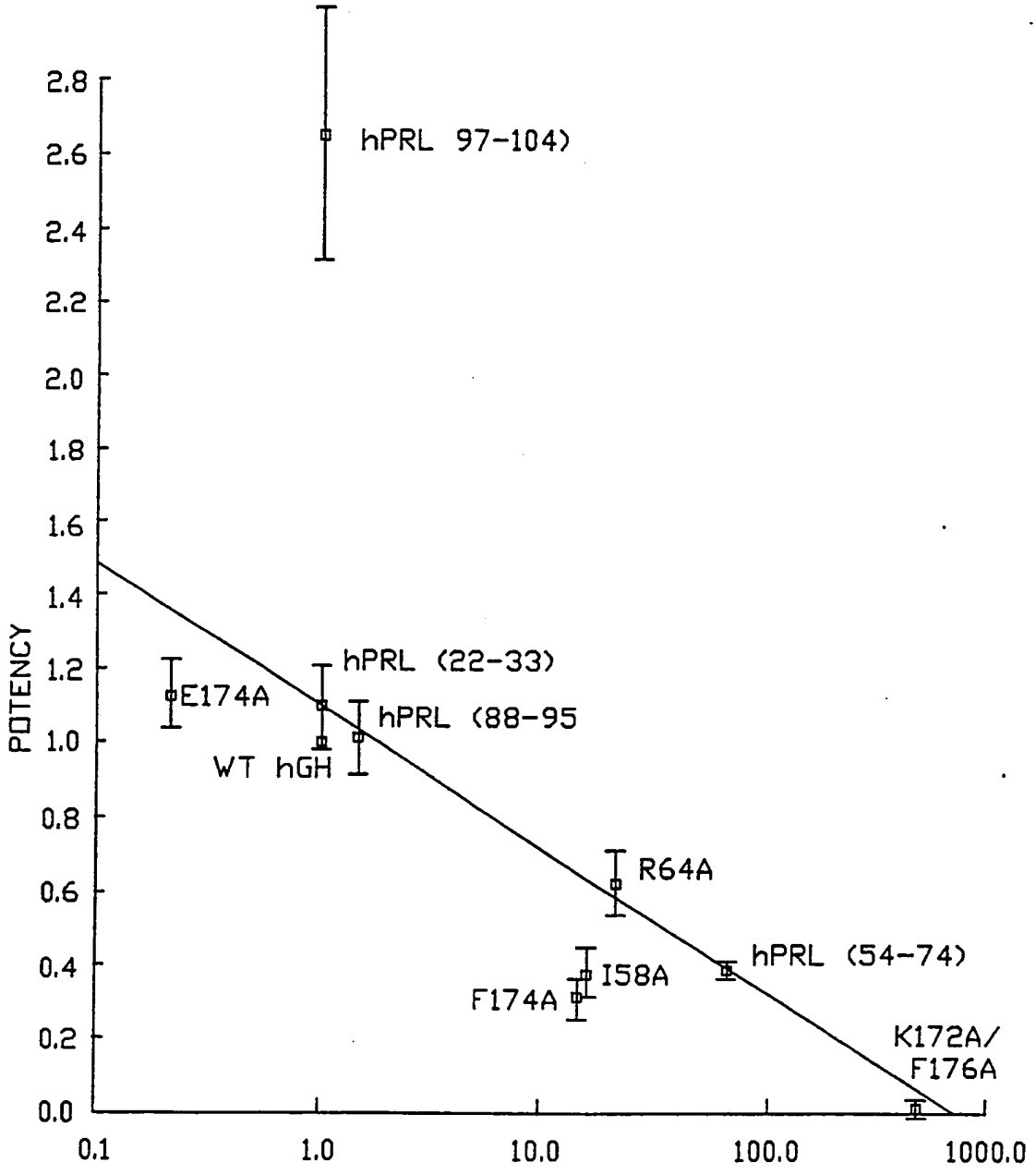


FIG.—23

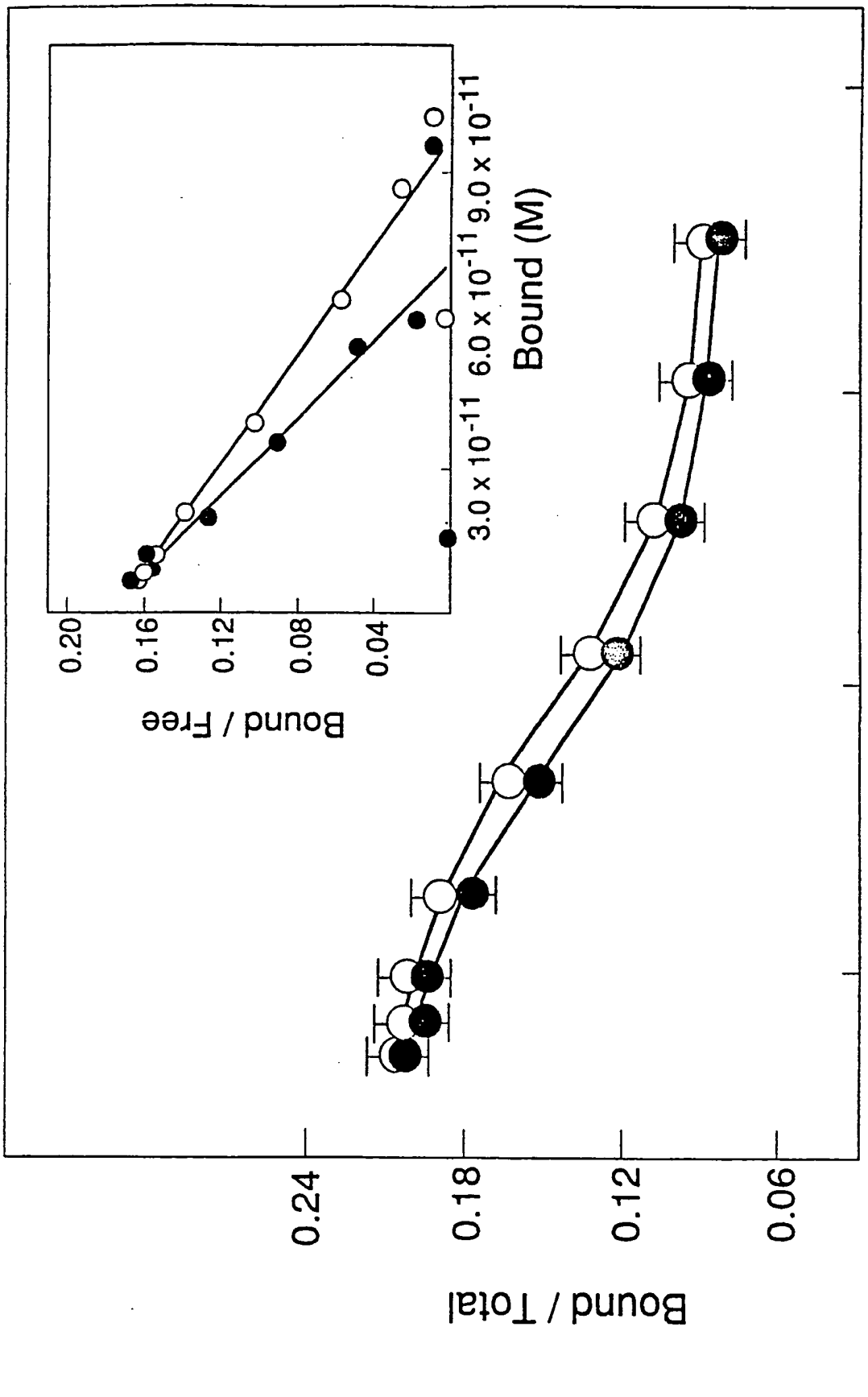

Bound / Total
0.24
0.18
0.12
0.06
10^{-10}
10^{-9}
10^{-8}
10^{-7}
Total (M)
Bound (M)
3.0×10^{-11}
6.0×10^{-11}
9.0×10^{-11}
Bound / Free
0.20
0.16
0.12
0.08
0.04

FIG.—24

Binding Determinants for hGHr

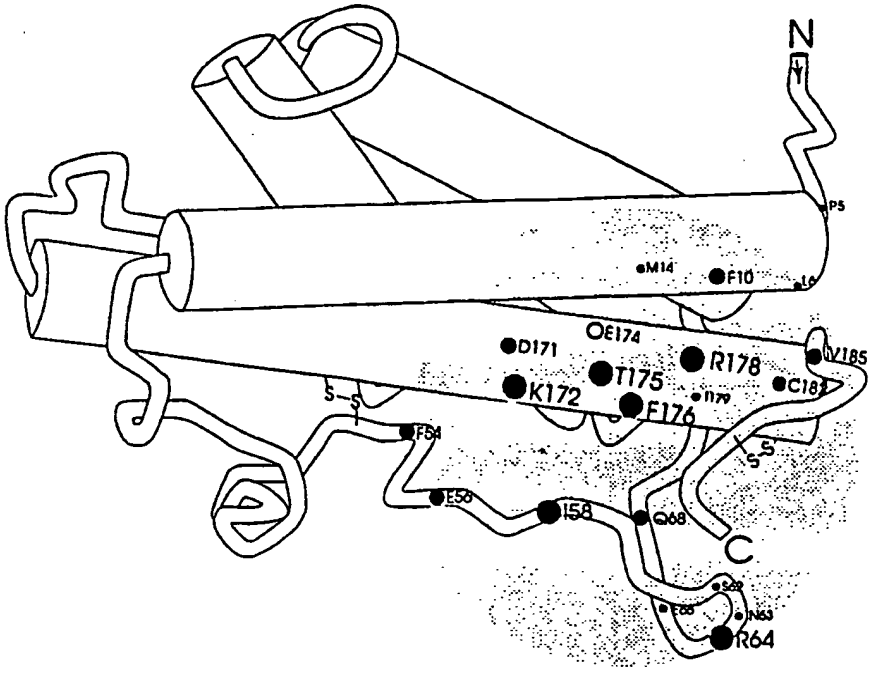


FIG.—25A

Binding Determinants for hPRLr

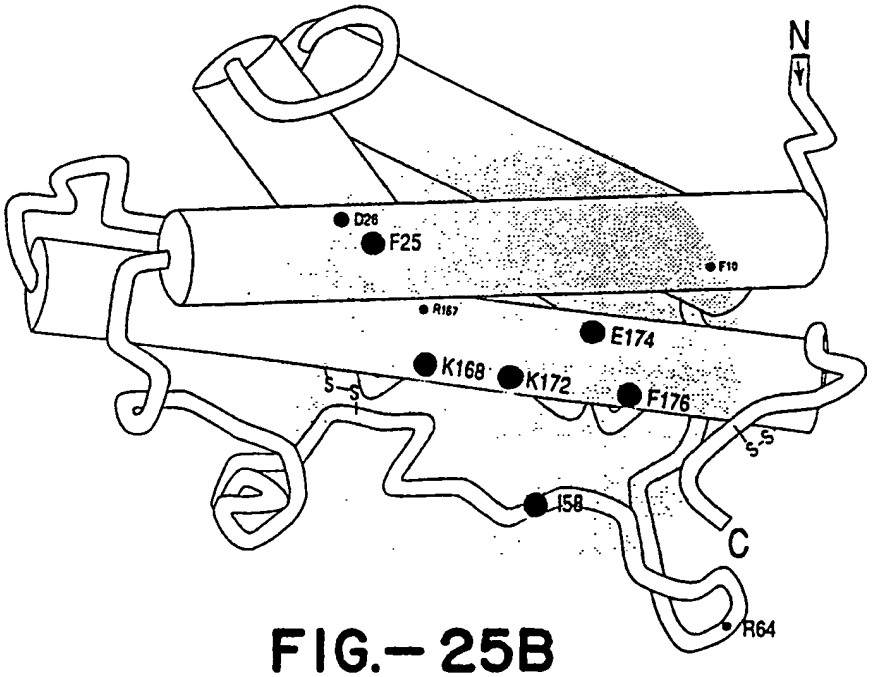


FIG.—25B

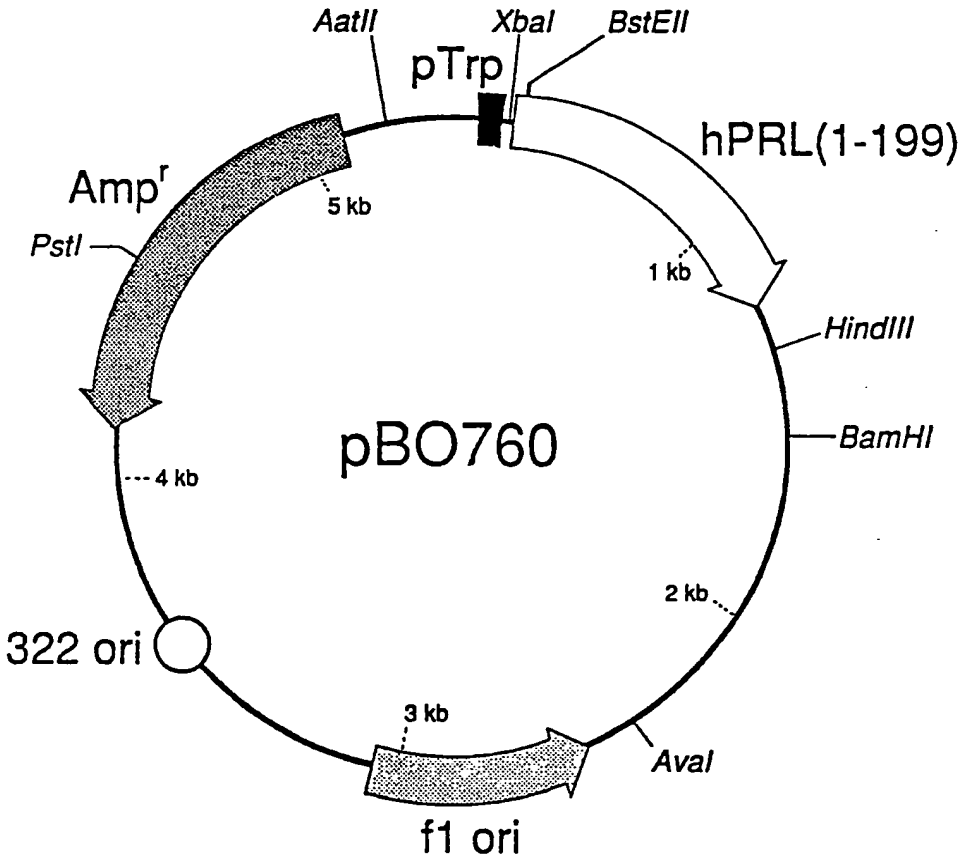

AatII
XbaI
BstEII
pTrp
hPRL(1-199)
Amp^r
5 kb
PstI
1 kb
HindIII
BamHI
pBO760
4 kb
2 kb
322 ori
3 kb
AvaI
f1 ori

FIG.—26

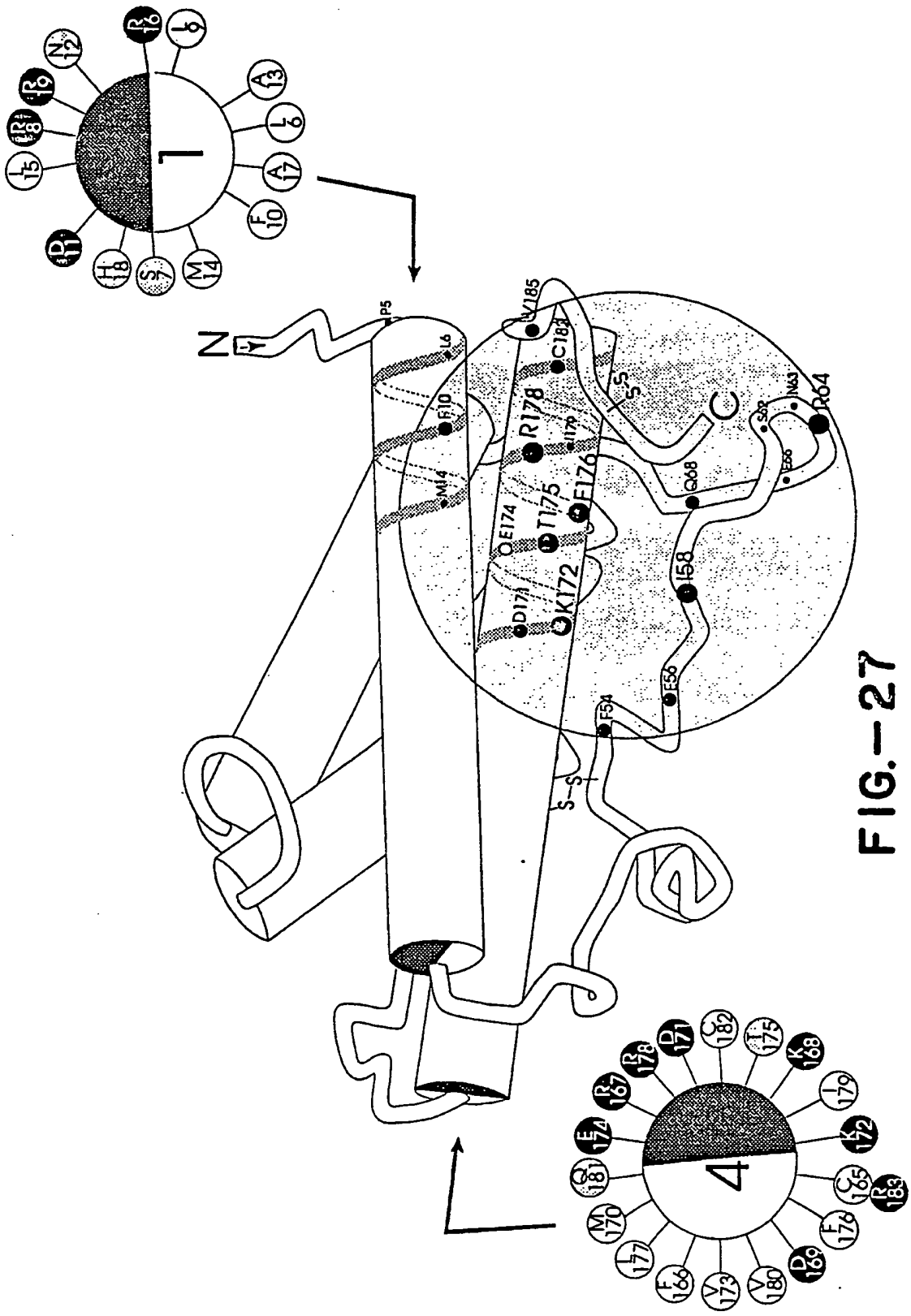

1
4
N
C
P5
L6
F10
M14
V185
C183
R178
I179
E176
T175
E174
K172
D171
158
E56
F54
S-S
S5
S52
N63
R64
Q68
E66

FIG.-27

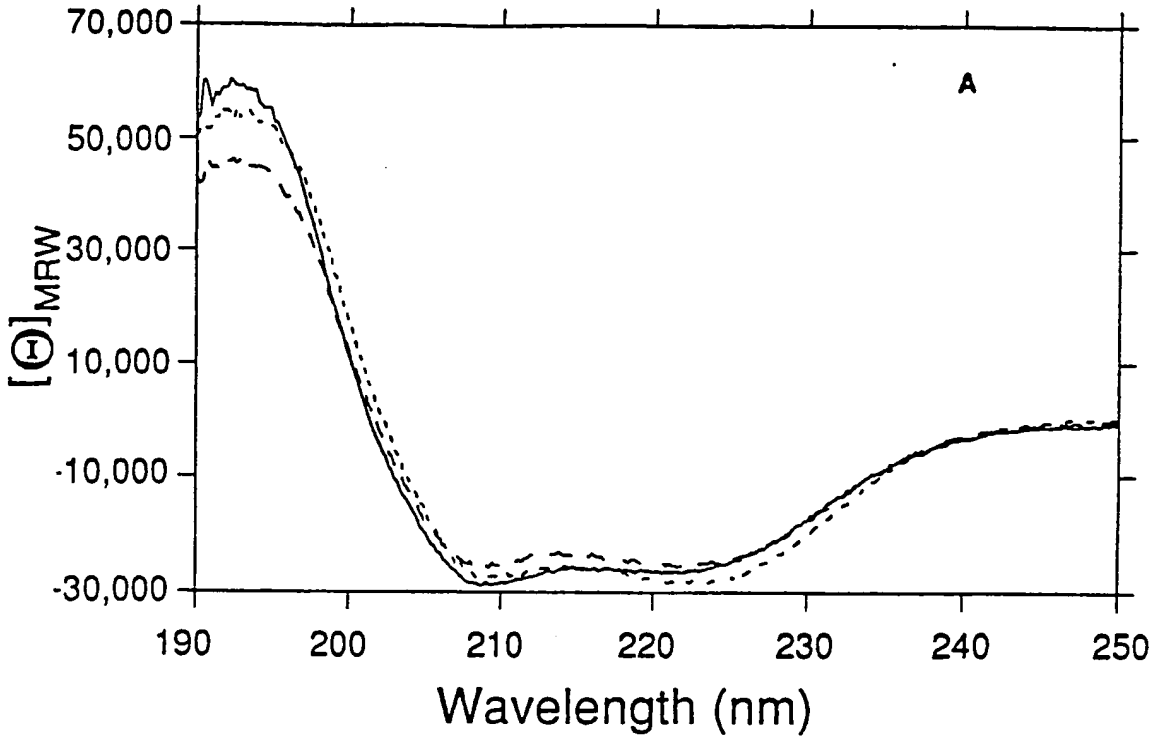


FIG.—28A

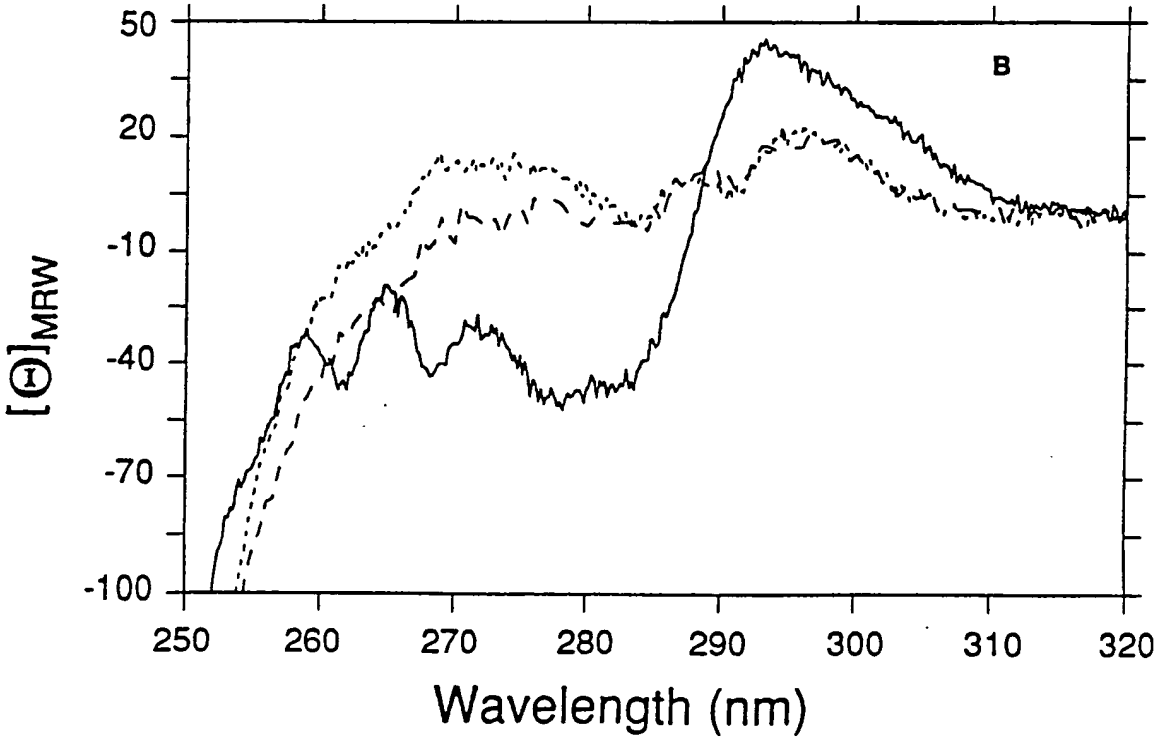


FIG.—28B

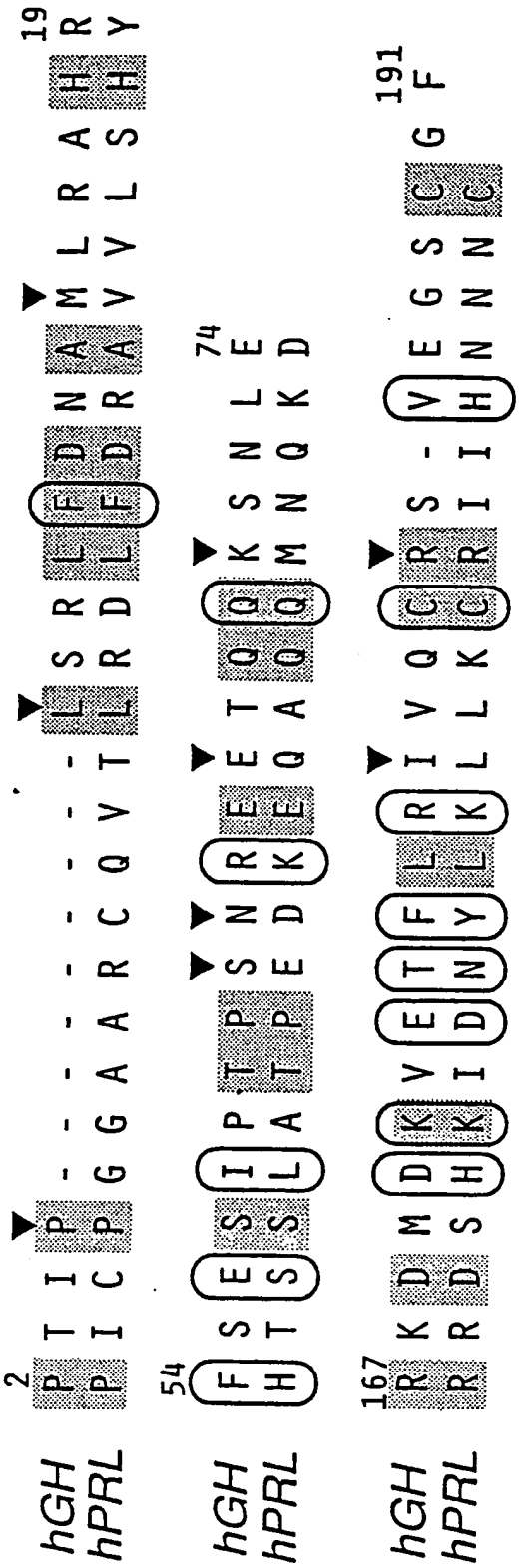

hGH
hPRL
2
P T I P - - - - - - - - - - - - - - - - - - -
P I C P G G A A R C Q V T L S R E F D N A M
L R D L F D R A V V L S H H R Y
54
F S E S I P T P S N R E E T Q Q K S N L E E
H T S S L A T P E D K E Q A Q Q M N Q K D D
167
R K D M D K V E T F L R I V Q C R S - V E G S C G F
R R D S H K I D N Y L K L L K C R I I H N N C

FIG.—29

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US89/04778

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): G01N 33/53,31/00; 33/543, 33/567, 33/566

U.S. Cl: 435/7; 436/501, 504, 518, 548

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	435/7; 436/501, 504, 518, 548; 935/79, 81

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

CHEMICAL ABSTRACTS SERVICE ONLINE, BIOSIS PREVIEWS, AUTOMATED PATENT SYSTEM

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X,P	Science, Volume 244, issued 1989, CUNNINGHAM, B.C., ET AL, "High Resolution Epitope Mapping of hGH-Receptor Interactions by Alanine-Scanning Mutagenesis", 1081-1085.	1-13,16-31
X,P	Science, Volume 243, issued 1989, CUNNINGHAM, B.C., ET AL, "Receptor and Antibody Epitopes in Human Growth Hormone Identified by Homolog-Scanning Mutagenesis", 1330-1336.	1-13,16-31
A	Biochem. Biophys. Res. Commun., Volume 135, issued 1986, SOUROUTON, M.C., ET AL, "Localization of a Highly Immunogenic Region on the Acetylcholine Receptor Alpha-Subunit", 82-89.	1-13,16-31

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
02 February 1990	05 MAR 1990
International Searching Authority	**Signature of Authorized Officer**
ISA/US	KAREN I. KRUPEN

Form PCT/ISA/210 (second sheet) (Rev.11-87)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	Endocrinol., Volume 121, issued 1987, WERTHER ET AL, "Localization and Characterization of Insulin Receptors in Rat Brain and Pituitary Gland Using In-Vitro Autoradiography and Computerized Densitometry, 1562-1570.	1-13,16-31
A	Endocrinology, Volume 107, issued 1980 MILLS, T.B. ET AL, "Fragments of human growth hormone produced by digestion with thrombin: chemistry and biological properties", 391-399 (See Abstract, 143544)	1-13,16-31
A	Chemical Abstracts, Volume 108, no. 11, issued 1988, (Columbus, Ohio, U.S.A) B. C. Cunningham, "Improvement in the alkaline stability of subtilisin using an efficient random mutagenesis and screening procedure", Abstract.	1-13,16-31

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . ... . , because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers..... , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

3. ☐ Claim numbers_____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

(See Attachment).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers: 1-13 and 16-31

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ATTACHMENT TO PCT/ISA/210
Part IV. Before #1, Observations

I. Claims 1-13 and 16-31 are drawn to a method for identifying unknown active domains in the amino acid sequence of polypeptides classified in class 436, subclass 501.

II. Claims 14, 15 and 32-64 are drawn to a method of forming a growth hormone variant and the growth hormone variants produced classified in class 530, subclass 350.

III. Claims 65-79 are drawn to human prolactin hormone variants classified in class 530, subclass 399.

IV. Claims 80-83 are drawn to human placental lactogen variants classified in class 530, subclass 399.

V. Claims 84-86 are drawn to DNA sequences and expression vectors and hosts classified in class 536, subclass 27.